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(54) Title: ISOPRENYL TRANSFERASE INHIBITORS

(57) Abstract

Peptidomimetic compounds useful in the treatment of Ras-associated human cancers, and other conditions mediated by farnesylated or geranylgeranylated proteins; and synthetic intermediates thereof.

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ISOPRENYL TRANSFERASE INHIBITORS

Background of the Invention

This invention concerns peptidomimetics useful in the treatment of human cancers.

Ras is an oncogene prevalent in over 20% of all human cancers. In particular, ras oncogenes are found in approximately 30% of all lung cancer, 30% of all myeloid leukemia, 50% of all colorectal carcinoma, and 90% of all pancreatic carcinoma. Barbacid, M., *Ann. Rev. Biochem.*, *56*:779 (1987), Bos, J.L., *Cancer Res.* *49*:4682 (1989). Examples of ras mutations include H-ras, K-ras, and N-ras.

Like other members of the superfamily of small GTP-hydrolyzing proteins, ras-encoded proteins require post-translational processing for membrane association and biological function. Maltese, W.A., *FASEB Journal*, *4*:3319 (1990), Hancock, J.F. et al., *Cell*, *57*:1167 (1989).

The post-translational processing of the ras protein is signalled by a short carboxy terminus consensus sequence, a CAAX box, indicating which isoprenyl group (farnesyl or geranylgeranyl) is to be attached. For farnesylated proteins, such as Ras, lamin B, and γ-transducin, C is cysteine, A is an aliphatic amino acid, and X is methionine, serine, or glutamine. Geranylgeranylated proteins such as Rap, Rab, Rho and other small GTP-binding proteins, have

similar CAAX sequences in which X is usually leucine, or occasionally phenylalanine.

Post-translational processing of the ras-encoded protein includes at least three steps. First, reaction with farnesyl pyrophosphate attaches a farnesyl group to the Cys^{186} residue. Second, a specific protease cleaves the three carboxy-terminal amino acids. Third, the carboxylic acid terminus is methylated to a methyl ester. The farnesyl transferase enzyme (FTase) mediates the attachment of the farnesyl group to a protein. The geranylgeranyl transferase I enzyme (GGTase) mediates the attachment of the geranylgeranyl group to a protein.

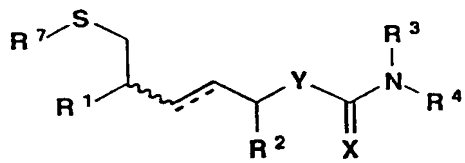
Post-translational processing, particularly farnesylation, of ras proteins is critical for *in vivo* ras protein function. Upstream of FTase, farnesylation of a ras protein can be inhibited by mevalonate synthesis inhibitors such as lovastatin or compactin, which are HMG-CoA reductase inhibitors. Direct inhibition of FTase by short peptides or peptide-like substrates has also been demonstrated.

Summary of the Invention

This invention features peptidomimetics useful in the treatment of ras-associated human cancers. The compounds of the invention inhibit post-translational modification of ras proteins by FTase, thereby down-regulating ras protein function. Substitution at the R^7, R^2, R^4 or R^5 positions (see, e.g., formula I below) modulates the specificity and selectivity of a compound of the invention for FTase and GGTase. The compounds of the invention inhibit post-translational modification of ras proteins by the related GGTase, which also results in down-regulation of ras protein function. Certain compounds of

the invention are selective or specific for FTase, in preference over GGTase.

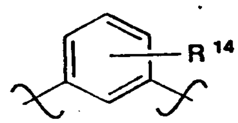
In general, the invention features a compound of the formula:



(I)

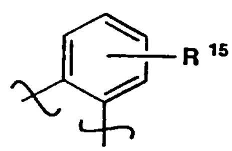
wherein R^1 is H, NHR^8, or NR^8R^9, wherein R^8 is H, C_{1-6} alkyl, C_{1-6} acyl, C_{2-14} alkyloxycarbonyl or any other amino-protecting group, and R^9 is C_{1-6} alkyl, C_{1-6} acyl, or C_{2-14} alkyloxycarbonyl; or, when taken together with R^7, a bifunctional organic moiety of fewer than 50 carbon atoms; R^2 is H, C_{1-8} alkyl, (C_{6-40} aryl)(C_{0-6} alkyl), or (C_{3-10} heteroaryl)(C_{0-6} alkyl); R^3 is H, C_{1-6} alkyl, or (C_{6-40} aryl)(C_{0-6} alkyl); R^4 is C_{3-16} cycloalkyl, (C_{3-16} heterocyclic radical)(C_{0-6} alkyl), (C_{6-12} aryl)-(C_{0-6} alkyl), (C_{3-16} heteroaryl)(C_{0-6} alkyl), C_{2-14} alkoxycarbonyl (or, where X is 2 singly-bonded H, any other amino-protecting group), R^5(CH-)(C=O)R^6, R^5(CH-)(C=S)R^6, R^5(CH-)(CH_2)R^6, or R^5(CH_2-), wherein R^5 is C_{1-6} alkyl, (C_{3-10} heterocyclic radical)(C_{0-6} alkyl), (C_{3-10} heteroaryl)(C_{1-6} alkyl), hydroxymethyl, $-(CH_2)_n-A-(CH_2)_m-CH_3$, $-(CH_2)_n(C{=}O)NH_2$, or $-(CH_2)_n(C{=}O)NH(CH_2)_mCH_3$ (wherein A is O, S, SO, or SO_2, n is 0, 1, 2 or 3, and m is 0, 1, or 2), or any other side chain of a naturally occurring amino acid; and R^6 is H, NH_2, NHOH, C_{3-16} heterocyclic radical, C_{3-16} heteroaryl, $NR^{10}R^{11}$, OR^{12}, $NR^{10}OR^{11}$, $NHOR^{13}$, or any other carboxyl-protecting group (e.g., where R^4 is R^5(CH-)(C=O)R^6, and R^6 is, e.g., OR^{12}) or any other hydroxyl protecting group (e.g., where R^4 is R^5(CH-)(CH_2)OR^{12}); wherein each of R^{10} and R^{11},

independently, is H, C_{1-6} alkyl, (C_{3-16} heterocyclic radical)(C_{0-6} alkyl), or (C_{3-16} heteroaryl)(C_{0-6} alkyl), R^{12} is H, C_{1-6} alkyl, (C_{1-12} acyl)oxy(C_{1-12} alkyl), (C_{1-12} alkyl)oxy(C_{1-12} alkyl), C_{2-14} alkyloxycarbonyl, or where R^4 is R^5(CH-)(CH_2)R^6, any other amino-protecting group, and R^{13} is H, C_{1-6} alkyl, or (C_{6-40} aryl)(C_{0-6} alkyl); X is =O, =S, or two singly-bonded H; Y is selected from the following five formulae:



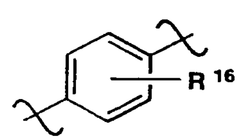
(i)

wherein R^{14} is H, halide, hydroxy, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-12} alkoxy, C_{1-6} acyloxy, C_{1-6} acyl, C_{6-41} aryl, C_{3-40} heterocyclic radical, C_{3-40} heteroaryl, C_{1-12} alkylsulfonyloxy, C_{1-12} haloalkylsulfonyloxy, C_{6-40} arylsulfonyloxy, or C_{6-41} aryloxy;



(ii)

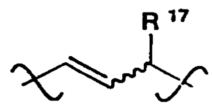
wherein R^{15} is H, halide, hydroxy, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-12} alkoxy, C_{1-6} acyloxy, C_{1-6} acyl, C_{6-41} aryl, C_{3-40} heterocyclic radical, C_{3-40} heteroaryl, C_{1-12} alkylsulfonyloxy, C_{1-12} haloalkylsulfonyloxy, C_{6-40} arylsulfonyloxy, or C_{6-41} aryloxy;



(iii)

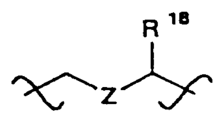
wherein R^{16} is H, halide, hydroxy, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-12} alkoxy, C_{1-6} acyloxy, C_{1-6} acyl, C_{6-41} aryl, C_{3-40} heterocyclic radical, C_{3-40} heteroaryl,

C_{1-12} alkylsulfonyloxy, C_{1-12} haloalkylsulfonyloxy, C_{6-40} arylsulfonyloxy, or C_{6-41} aryloxy;



(iv)

wherein R^{17} is H, C_{1-8} alkyl, (C_{6-40} aryl)(C_{0-6} alkyl), (C_{3-10} heteroaryl)(C_{0-6} alkyl), or (C_{3-10} heterocyclic radical)(C_{0-6} alkyl); and



(v)

wherein R^{18} is H, C_{1-8} alkyl, (C_{6-40} aryl)(C_{0-6} alkyl), (C_{3-10} heterocyclic radical)(C_{0-6} alkyl), or (C_{3-10} heteroaryl)(C_{0-6} alkyl), and Z is O, S, SO, SO_2, or NR^{19} wherein R^{19} is H, C_{1-6} alkyl, C_{1-6} acyl, (C_{6-40} aryl)-(C_{0-6} alkyl), C_{3-10} heterocyclic radical, (C_{3-10} heteroaryl)-(C_{0-6} alkyl), or C_{2-14} alkyloxycarbonyl; or wherein R^{18} and NR^{19} taken together form a bifunctional C_{6-40} aryl, a bifunctional C_{3-12} heterocyclic radical, or a bifunctional C_{3-12} heteroaryl; and R^7 is an organic moiety having fewer than 50 carbon atoms or, when taken together with R^1, a bifunctional organic moiety having fewer than 50 carbon atoms; or a pharmaceutically acceptable salt thereof.

Compounds of the invention include, for example, compounds PD301, PD311, PD321, PD331, PD341, PD351, PD361, PD371, PD381, PD391, PD401, PD411, PD421, PD431, PD441, PD451, PD461, PD012, PD022, PD032, PD042, PD052, PD062, PD072, PD082, PD092, PD102, PD112, PD132, PD142, PD152, PD162, PD172, PD182, PD192, PD202, PD212, PD222, PA011, PA021, PA031, PA041, PA051, PA061, PA071, PA081, PA091, PA101, PA111, PA121, PA131, PA141, PE011, PE021, PE031,

PE041, PE051, PE061, PT011, PM011, PM021, PM031, PM041, PM051, PM061, PM071, PM081, PM091, PM101, PM111, PM121, PM131, PM141, PM151, PM161, PM012, PM022, PM032, PM042, PM052, PM062, PM072, PM082, PM092, PM102, PM112, PM122, PM132, PM142, PM152, PM162, PM172, PM182, PM192, PM202, PM212, and PM222.

In one aspect of the invention, compounds of the invention inhibit post-translational modification of the oncogenic ras protein by FTase, GGTase, or both. Such inhibition reduces or blocks the ability of the ras protein to transform normal cells to cancer cells. Compounds of formulae I-VI and VIII-XI, therefore, are for use in medicine (e.g., treatment of conditions mediated by farnesylated or geranylgeranylated proteins, such as treatment of ras-associated tumors, in mammals, e.g., humans).

Examples of ras-associated tumors include: tumors of the bladder, breast, colon, kidney, liver, lung, ovary, pancreas, and stomach; hematopoietic tumors of lymphoid (acute lymphocytic leukemia, B-cell lymphoma, Burkitt's lymphoma) and myeloid (acute and chronic myelogenous leukemias, promyelocytic leukemia) origins; in tumors of mesenchymal origin (such as fibrosarcomas and rhabdomyosarcomas); and melanomas, teratocarcinomas, neuroblastomas, gliomas, and keratoacanthomas (see supra, Barbacid, 1987).

In another aspect, the invention encompasses methods of treating ras-associated tumors in a patient by administering an effective amount of a pharmaceutical formulation of one or more compounds of the invention to the patient.

In another aspect, the invention encompasses synthetic intermediates of the disclosed inhibitor compounds

such as compounds R007D, R011D, R019D, R020D, R029D, R003E, R005E, R004T, R003M-R006M, R025M, R027M, R023D, R017M, R006A, R004A, R003A, R012A, R014D, R023M, R024D, R007E, R001A, R007T, R013D, R018M, and Wittig reagent R012M.

Other features and advantages of the present invention will be apparent from the following drawings and detailed description, and also from the appending claims.

Detailed Description

A. Abbreviations

Abbreviations used herein unless otherwise specified are: BOC or *t*-BOC (t-butoxycarbonyl); BOC_2O or $tBOC_2O$ (di-*t*-butyldicarbonate); CMC (1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate); COD (1,5-cyclooctadiene); DCC (dicyclohexylcarbodiimide); DIBAL (diisobutylaluminum hydride); DMAP (4-dimethylaminopyridine); DME (1,2-dimethoxyethane); DMF (dimethylformamide); EDC (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide); FC (flash chromatography on silica gel); HMDS (hexamethyldisilazide, also known as bis(trimethylsilyl)amide); HOBT (hydroxybenzotriazole hydrate); HPLC (high pressure liquid chromatography); MTT ([3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2*H*-tetrazolium bromide]); NMM (*N*-methylmorpholine); PNB (*p*-nitrobenzyl); RP (reversed phase); TBAF (tetrabutylammonium fluoride); TBS (*t*-butyldimethylsilyl); TFA (trifluoroacetic acid); Tf (trifluoromethanesulfonyl); Tf_2O (trifluoromethanesulfonic anhydride); THF (tetrahydrofuran); TsCl (*p*-toluenesulfonyl chloride); and TsOH (*p*-toluenesulfonic acid monohydrate).

B. Terms

An alkyl group is a branched or unbranched hydrocarbon that may be substituted or unsubstituted. Examples of branched alkyl groups include isopropyl, *sec*-butyl, isobutyl, *tert*-butyl, *sec*-pentyl, isopentyl, *tert*-pentyl, *sec*-hexyl, isohexyl, and *tert*-hexyl. Substituted alkyl groups may have one, two, three, or more substituents, which may be the same or different, each replacing a hydrogen atom. Substituents are halide, hydroxyl, protected hydroxyl, amino, protected amino, carboxy, protected carboxyl, cyano, methylsulfonylamino, alkoxy, acyloxy, nitro, and lower haloalkyl.

Similarly, cycloalkyl, aryl, arylalkyl, alkylaryl, heteroaryl, and heterocyclic radical groups may be substituted with one or more of the above substituting groups. Examples of cycloalkyl groups are cyclopropyl, cyclopentyl, cyclohexyl, and cyclooctyl. An aryl group is a C_{6-40} aromatic ring, wherein the ring is made of carbon atoms (e.g., C_{6-20}, or C_{6-12} aryl groups).

A heterocyclic radical contains at least one ring structure which contains carbon atoms and at least one heteroatom such as N, O, or S. A heteroaryl is an aromatic heterocyclic radical. Examples of heterocyclic radicals and heteroaryl groups include: thiazolyl, 2-thienyl, 3-thienyl, 3-furyl, furazanyl, 2H-pyran-3-yl, 1-isobenzofuranyl, 2H-chromen-3-yl, 2H-pyrrolyl, *N*-pyrrolyl, imidazolyl, pyrazolyl, isothiazolyl, isoxazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolizinyl, isoindolyl, indolyl, indazolyl, purinyl, phthalazinyl, cinnolinyl, and pteridinyl.

A heterocyclic radical may be attached to another moiety via a carbon atom or a heteroatom of the heterocyclic radical. In formulae I-III where R^6 is a heterocyclic

radical or heteroaryl, R^6 is preferably attached to a thionyl or carbonyl of R^4 via a heteroatom of R^6. This preference extends analogously to generic formulae IV-VI where R^{26} is a heterocyclic radical or heteroaryl, R^{26} is preferably attached to a thionyl or carbonyl of R^{24} via a heteroatom of R^{26}. This preference also extends analogously to formulae VIII-XI.

In certain embodiments, R^4 (and analogous groups such as R^{24}) may be a lactone or lactam (or the thiocarbonyl or thioester equivalents). For example, R^4 includes radicals of homoserine lactone and homocysteine lactone.

An acyl group has the formula R(C=O)- and an acyloxy group has the formula R(C=O)-O-, wherein R is H, C_{1-12} alkyl, C_{6-20} aryl, or C_{7-20} arylalkyl. Thus, a C_{1-14} acyl includes R being, for example, H, C_{1-6} alkyl, C_{6-12} alkyl, and C_{7-13} arylalkyl. An alkyloxyalkyl group has the formula R-O-R'-, wherein each of R and R', independently, is C_{1-12} alkyl (e.g., R is C_{1-8} or C_{1-6}). An acyloxyalkyl group has the formula R-(C=O)-O-R'-, wherein each of R and R', independently, is C_{1-12} alkyl, C_{6-20} aryl, or C_{7-20} arylalkyl (e.g., is C_{1-8} or C_{1-6}). An alkyloxycarbonyl group has the formula R-O-(C=O)-, wherein R is C_{2-14} alkyl (eg., C_{2-6}). A preferred alkyloxycarbonyl group is *t*-butoxycarbonyl (BOC). A carbamoyl group has the formula RR'N-(C=O)-, wherein each of R and R', independently, is H, C_{1-12} alkyl, or C_{6-20} aryl.

An activated leaving group (L, L^n) departs from a substrate with the pair of electrons of the covalent bond between the leaving group and the substrate; preferred leaving groups stabilize those electrons via the presence of electron-withdrawing groups, aromaticity, resonance structures, or a combination thereof. Examples of activated

(or electron-withdrawing) leaving groups include halide (iodide and bromide are preferred); hydroxy; C_{1-12} alkylsulfonyloxy such as mesylate and trifluoromethanesulfonate; C_{6-20} arylsulfonyloxy such as *p*-toluenesulfonate, *p*-nitrobenzenesulfonate; benzoate and benzoate derivatives such as *p*-nitrobenzoate; C_{7-40} arylalkyl such as *p*-nitrobenzyl; C_{7-20} arylalkyloxy; C_{1-12} alkoxy; C_{2-12} alkyloxycarbonyl such as BOC; C_{1-12} acyloxy, C_{1-12} carbamoyl, and C_{2-5} haloalkylcarbonyloxy such as trifluoroacetate. Examples of electron-withdrawing groups include halides, halogenated alkyls, carboxylate, and nitro groups.

Numerous thiol-, amino- and carboxyl-protecting groups are well-known to those in the art. In general, the species of protecting group is not critical provided that it is stable to the conditions of any subsequent reaction(s) on other positions of the compound and can be removed at the appropriate point without adversely affecting the remainder of the molecule. In some embodiments, R^1 and R^7 taken together are preferably a bifunctional thiol-protecting group, having two points of attachment instead of one, such as -(C=O)- and isopropylidene ($-C(CH_3)_2-$) which form particularly stable products.

Similarly, in some embodiments, R^{18} and NR^{19} taken together are a bifunctional aryl, heteroaryl, or heterocyclic radical. Examples of preferred thiol-protecting groups include thioethers, sulfenyl derivatives, disulfides, and bifunctional protecting groups such as dithiols, aminothiols, thioaminals, and thioacetals, such as thiazolidines and thiazolidinones. A preferred thiol-protecting group, such as a disulfide, will be cleaved under mild reductive conditions.

Examples of disulfides include *S*-ethyl, *S*-*t*-butyl, and substituted *S*-phenyl. In addition, symmetrical and asymmetrical disulfides are discussed further below.

Examples of thioethers include (i) *S*-benzyl and derivatives thereof such as *S*-4-methyl- and *S*-3,4-dimethylbenzyl, *S*-*p*-methoxybenzyl, *S*-*o*- or *p*-hydroxybenzyl (or acetoxybenzyl), *S*-*p*-nitrobenzyl, *S*-4-picolyl, *S*-2-picolyl *N*-oxide, and *S*-9-anthrylmethyl; (ii) *S*-diphenylmethyl, substituted *S*-diphenylmethyl, and *S*-triphenylmethyl (*S*-trityl) thioethers such as *S*-diphenyl-4-pyridylmethyl, *S*-5-dibenzosuberyl, and *S*-bis(4-methoxyphenyl)methyl, and ; (iii) substituted *S*-methyl derivatives such as *S*-methoxymethyl, *S*-isobutoxymethyl, *S*-2-tetrahydropyranyl, *S*-benzylthiomethyl, thiazolidines, *S*-acetamidomethyl, *S*-benzamidomethyl, *S*-acetyl-, *S*-carboxy-, and *S*-cyanomethyl; and (iv) substituted *S*-ethyl derivatives such as *S*-2-nitro-1-phenylethyl, *S*-*t*-butyl, *S*-2,2-bis(carboethoxy)ethyl, and *S*-1-*m*-nitrophenyl-2-benzoylethyl.

Thioesters including *S*-acetyl, *S*-benzoyl, thiocarbonates (e.g., *S*-benzyloxycarbonyl, *S*-*t*-butoxycarbonyl), and thiocarbamates (e.g., *S*-(*N*-ethyl)) and *S*-(*N*-methoxymethyl) are less preferred for use in the synthetic pathway shown. For example, some of these thioesters and thiocarbamates may not be resistant to the LiOH/MeOH/H_2O hydrolysis in Scheme VIII. However, an organic chemist of ordinary skill can make suitable modifications to the synthetic pathway, such as using an ester other than methyl, to improve the compatibility of these thiol-protecting groups.

In addition, a protecting group may be substituted for another after substantive synthetic transformations are complete. Clearly, where a compound differs from a compound disclosed herein only in that one or more protecting groups

of the disclosed compound has been substituted with a different protecting group (e.g., carbamate), that compound is within the invention. Further examples and conditions for thiol-, amino-, and carboxyl-protecting group chemistry are found in T.W. Greene, *Protective Groups in Organic Synthesis*, (1st ed., 1981, 2nd ed., 1991).

The invention also encompasses isotopically-labelled counterparts of compounds disclosed herein. An isotopically-labelled compound of the invention has one or more atoms replaced with an isotope having a detectable particle-emitting (radioactive) nucleus or a magnetogyric nucleus. Examples of such nuclei include but are not limited to ^{2}H, ^{3}H, ^{13}C, ^{14}N, ^{19}F, ^{29}Si, ^{31}P, and ^{32}P. Isotopically-labelled compounds of the invention are particularly useful as probes or research tools for spectrometric analyses, radioimmunoassays, binding assays based on γ- or β- scintillation, autoradiography, and kinetic studies such as the determination of primary and secondary isotope effects.

C. Embodiments

It will be apparent to those in the art that formulae I and IV are closely related, having substituents which are analogous. For example, R^1, R^5 and R^7 in formula I are analogous to R^{21}, R^{25}, and R^{27} in formula IV, respectively. Thus, in this description, general guidance and preferred embodiments described for R^1 are understood to apply to R^{21}, those for R^7 are understood to apply to R^{27}, and so on. In addition, those in the art will recognize other relationships, such as that formula I is closely related to formulae II and III; that formulae (i)-(v) are closely related to formulae (vi)-(x); and that formulae VII-XI are related to formulae I and IV.

In one aspect, the invention is a compound having a formula selected from formulae I-III (or IV-VI), where R^7 (or an analogous group such as R^{27} in formula IV) is any moiety compatible with the intended use of the compound. In one aspect, a compatible moiety is an organic moiety having fewer than 100 carbon atoms, such as fewer than 50, 35, 30 or 20 carbon atoms. In another aspect, a compatible moiety is a polymer backbone or matrix for drug release or delivery, which may contain 100, 150, or more carbon atoms, due to its polymeric nature.

A compatible organic moiety must not interfere with the intended use of the compound. For example, where the use is inhibition of one or more isoprenyl transferase enzymes, the remainder moiety may enhance the inhibition; perform a supplementary ras-associated function; perform a complementary different function; or perform no particular function, including undergoing chemical cleavage from the inhibitor moiety of the compound in the body.

Examples of an organic moiety include mono- or bifunctional thiol-protecting groups; detectable or bioimaging agents; systemic or specific anti-cancer agents; targeting agents intended to localize delivery of a compound of the invention to a selected class of cells, a tissue, or an organ; directing agents intended to selectively discourage uptake of a compound of the invention by a selected class of cells, a tissue, or an organ; other competitive, noncompetitive, uncompetitive or mixed inhibition inhibitors of an isoprenyl transferase enzyme. Such inhibitors include inhibitors of ras-associated enzymes, including suicide substrates of ras-associated enzymes.

In one aspect, the compound of the invention is a disulfide. An asymmetrical disulfide is a moiety set forth

in a formula selected from the formulae I-III wherein R^7 (or an analogous group such as R^{27} in formulae IV-VI) is deleted, the free sulfur atom being bonded to any moiety having a second reactive sulfur atom to form a disulfide. Preferably, "any moiety" is an organic moiety having fewer than 100 carbon atoms, such fewer than 50, 40, 30 or 20 carbon atoms. Examples of such organic moieties include but are not limited to the other moieties listed in a previous paragraph (such as detectable or bioimaging agents, anti-cancer agents, and drug-targeting agents) and the moieties defined by R^7, or R^7 and R^1 when taken together.

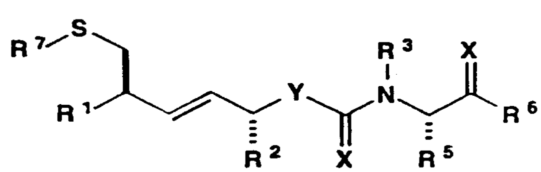
Another embodiment of this aspect relates to an asymmetrical disulfide, wherein the organic moiety is itself a (different) moiety set forth in a formula selected from the formulae I-VI wherein R^7 (or an analogous group such as R^{27} in formula IV) is deleted. In another embodiment, the invention relates to a symmetrical disulfide dimer, wherein R^7 is a moiety of the same formula with R^7 deleted, such as PD212, PE041, PE051, PM141, and PM022. Due to the reactivity of an unprotected thiol group, it may be desirable to store or handle a compound of the invention in the form of a symmetrical disulfide dimer or an asymmetrical disulfide.

Chemically-linked (e.g., disulfide) or formulated (mixture) combinations of two different compounds of the invention are useful not only to prevent premature sequestration in the patient, but also to formulate and deliver a dual-acting drug. For example, a first compound may be a more potent FTase inhibitor than a second compound and the second may be a more potent GGTase inhibitor than the first. Thus, to the extent that some farnesylated proteins may be alternatively geranylgeranylated, a GGTase

inhibitor will also be available in the patient via the same drug dose.

Certain compounds (in fact a majority) of the invention are dual-acting compounds, wherein the compound has some degree of activity for both GGTase and FTase. The relative selectivity and specificity can be modulated by substitution (e.g., at the R^7, R^2, R^4, R^5, and Y positions). Therefore, to the extent that some farnesylated proteins may be alternatively geranylgeranylated, a GGTase inhibitor will also be available in the patient via the same compound.

In general, the preferred stereochemistry for the $-CH_2-S-R^7$ moiety and for each of R^2 and R^5, independently, (and analogous groups such as R^{22}, R^{52}, and R^{76}; and R^{25}, respectively) is shown below. Note that a preferred species may have the indicated preferred stereochemistry at one, both, or neither of the R^2 and R^5 positions. Furthermore, while the invention encompasses both *cis* and *trans* geometries, *trans* is preferred at the carbon-carbon double bond shown below.



R^{14}, R^{15}, and R^{16} (and analogous groups such as R^{34}, R^{35}, and R^{36}, respectively) may be *ortho* ,*meta*, or *para* relative to a phenylene point of attachment.

The enzyme specificity of the inhibitor compounds of the invention is determined, in part, by the amino acid defined by the side chain of substituent R^5 (or analogous groups such as R^{25}). Generally, where the amino acid is one of the preferred amino acids (methionine, glutamine, or

serine), the inhibitor is specific for FTase. Where the amino acid defined by the side chain of substituent R^5 is another amino acid, in particular leucine and phenylalanine, the inhibitor will generally inhibit GGTase. Compounds which inhibit FTase are preferred for their specificity. Potency and specificity for FTase and GGTase can be measured by methods well known in the art, including those disclosed herein, such as the *in vitro* inhibition assays in Example A below.

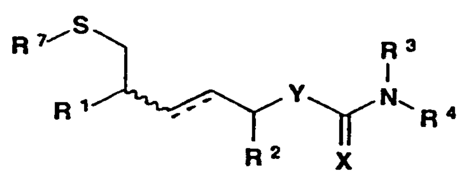
Preferred embodiments include compounds of formulae I-III (or IV-VI), wherein R^1 (or R^{21}) is NH_2 or NHR^8 (or NHR^{28}); R^8 (or R^{28}) is C_{1-6} acyl, C_{1-6} alkyl, or C_{2-8} alkyloxycarbonyl; R^2 (or R^{22}) is H, C_{1-8} alkyl, (C_{6-10} aryl)(C_{0-3} alkyl), or (C_{3-10} heteroaryl)(C_{0-3} alkyl); R^{17} (or R^{37}) is H, C_{1-8} alkyl, (C_{6-20} aryl)(C_{0-3} alkyl), (C_{3-10} heteroaryl)(C_{0-3} alkyl), or (C_{3-10} heterocyclic radical)(C_{0-3} alkyl); R^3 (or R^{23}) is H, C_{1-6} alkyl, or (C_{6-12} aryl)(C_{0-3} alkyl); R^4 (or R^{24}) is is C_{3-8} cycloalkyl, (C_{3-9} heterocyclic radical)(C_{0-3} alkyl), (C_{6-12} aryl)-(C_{0-3} alkyl), or (C_{3-9} heteroaryl)(C_{0-3} alkyl), R^5(CH-)(C=O)R^6 (or R^{25}(CH-)(C=O)R^{26}); wherein R^5 (or R^{25}) is C_{1-6} alkyl, (C_{3-9} heterocyclic radical)(C_{0-3} alkyl), (C_{3-9} heteroaryl)(C_{0-3} alkyl), (C_{0-3} alkyl)sulfonyl(C_{0-3} alkyl), (C_{0-3} alkyl)sulfoxide(C_{0-3} alkyl) or a side chain of an amino acid selected from the group glycine, alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, lysine, glutamic acid, glutamine, arginine, cysteine, methionine, phenylalanine, and proline; R^6 (or R^{26}) is H, NH_2, NHOH, NHR^{10} (or NHR^{30}), OR^{12} (or OR^{32}), C_{3-9} heterocyclic radical, C_{3-9} heteroaryl; wherein R^{10} (or R^{30}) is C_{1-6} alkyl; R^{12} (or R^{32}) is H, C_{1-6} alkyl, or

(C_{1-6} acyl)oxy(C_{1-6} alkyl); R^{14} (or R^{34}) is H, halide, hydroxy, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, (C_{6-10} aryl)(C_{0-3} alkyl), (C_{3-9} heterocyclic radical)-(C_{0-3} alkyl), (C_{3-9} heteroaryl)(C_{0-3} alkyl); R^{18} (or R^{38}) is H, C_{1-6} alkyl, (C_{3-9} heterocyclic radical)(C_{0-3} alkyl), (C_{3-9} heteroaryl)(C_{0-3} alkyl), or (C_{6-12} aryl)(C_{0-3} alkyl); R^7 (or R^{27}) is an organic moiety having fewer than 30 carbon atoms, and more preferably, H, a thiol-protecting group, or a moiety set forth in one of the formulae I-III (or IV-VI) wherein R^7 (or R^{37}) is deleted; or combinations of the above.

Certain embodiments include compounds of formulae I-III (or IV-VI), wherein R^1 (or R^{21}) is NH_2 or NH-(C_{1-6} acyl); R^2 (or R^{22}) is H, 2-butyl, *t*-butyl, isopropyl, or benzyl; R^3 (or R^{23}) is H or methyl; R^{17} (or R^{37}) is isopropyl or benzyl; R^4 (or R^{24}) is 2-butanolidyl, 2-pyridinyl, 4-oxa-pyrazin-*N*-yl, or R^5(CH-)(C=O)R^6 (or R^{25}(CH-)(C=O)R^{26}); wherein R^5 (or R^{25}) is (2-thiophenyl)methyl, methylsulfonylethyl, or a side chain of methionine (2-(methylmercapto)ethyl), glutamine ($-CH_2-CH_2-(C{=}O)-NH_2$), serine (hydroxymethyl), or leucine (isobutyl), and R^6 (or R^{26}) is NHR^{10} (or NHR^{30}), OR^{12} (or OR^{32}); R^{10} (or R^{30}) is *t*-butyl; R^{12} (or R^{32}) is H, methyl, ethyl, or isobutyl; R^{14} (or R^{34}) is methyl, ethyl, ethenyl, methoxy, ethoxy, propenyl, phenyl, benzyl, 2-furyl, 3-furyl, *o*-, *m*- or *p*-methoxyphenyl, *m*- or *p*-(trifluoromethyl)phenyl, 2-thienyl, 3-thienyl; R^{18} (or R^{38}) is 2-thienylmethyl, 2-butyl, or benzyl; R^7 (or R^{27}) is an organic moiety having fewer than 30 carbon atoms, and more preferably, H, a thiol-protecting group, or a moiety set forth in one of the formulae I-III (or IV-VI) wherein R^7 (or R^{37}) is deleted; or combinations of the above.

In certain embodiments, leaving group L^n is halide (iodide and bromide are preferred); hydroxy; C_{1-12} alkylsulfonyloxy such as mesylate and trifluoromethanesulfonate; C_{6-20} arylsulfonyloxy such as *p*-toluenesulfonate, *p*-nitrobenzenesulfonate; benzoate and benzoate derivatives such as *p*-nitrobenzoate; C_{1-12} carbamoyl; C_{1-12} acyloxy; C_{7-40} arylalkyl such as *p*-nitrobenzyl; C_{7-20} arylalkyloxy; C_{1-12} alkoxy; C_{2-12} alkyloxycarbonyl such as BOC; and C_{2-5} haloalkylcarbonyloxy such as trifluoroacetate.

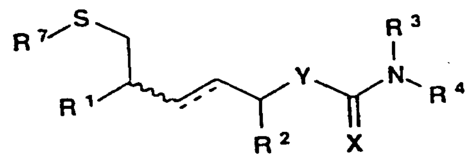
One embodiment is a compound of formula II:



(II)

wherein R^1 is H, NHR^8, or NR^8R^9, wherein R^8 is H, C_{1-6} alkyl, C_{1-6} acyl, C_{2-14} alkyloxycarbonyl or any other amino-protecting group, and R^9 is C_{1-6} alkyl, C_{1-6} acyl, C_{2-14} alkyloxycarbonyl or, when taken together with R^7, a bifunctional thiol-protecting group; and R^7 is H; a thiol protecting group or, when taken together with R^9, a bifunctional thiol-protecting group; or a moiety set forth in the above generic formula (II) wherein R^7 is deleted, said compound being a symmetrical disulfide dimer or an asymmetrical disulfide; or a pharmaceutically acceptable salt thereof.

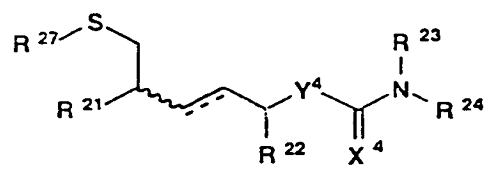
Another embodiment is a compound of formula III:



(III)

wherein R^1 is NHR^8 or NR^8R^9, wherein R^8 is C_{1-6} alkyl, C_{1-6} acyl, C_{2-14} alkyloxycarbonyl, or any other amino-protecting group, and R^9 is C_{1-6} alkyl, C_{1-6} acyl, C_{2-14} alkyloxycarbonyl or, when taken together with R^7, a bifunctional thiol-protecting group; R^6 is H, NH_2, NHOH, C_{3-10} heterocyclic radical, C_{3-10} heteroaryl, NHR^{10}, $NR^{10}R^{11}$, OR^{12}, $NR^{10}OR^{11}$, or $NHOR^{13}$, (wherein each of R^{10} and R^{11}, independently, is C_{1-6} alkyl, (C_{3-16} heterocyclic radical)(C_{0-6} alkyl), C_{2-14} alkyloxycarbonyl, or (C_{3-16} heteroaryl)(C_{1-6} alkyl)), R^{12} is C_{1-6} alkyl, (C_{1-12} acyl)oxy(C_{1-12} alkyl), (C_{1-12} alkyl)oxy(C_{1-12} alkyl), C_{2-14} alkyloxycarbonyl, or where R^4 is R^5(CH-)(C=O)OR^{12}, any other carboxyl-protecting group, or where R^4 is R^5(CH-)(CH_2)OR^{12}, any other hydroxyl-protecting group, and R^{13} is H, C_{1-6} alkyl, or (C_{6-40} aryl)(C_{0-6} alkyl); R^7 is a thiol-protecting group, or, when taken together with R^9, a bifunctional thiol-protecting group; or a moiety set forth in the above generic formula (III) wherein R^7 is deleted, said compound being a symmetrical disulfide dimer or an asymmetrical disulfide.

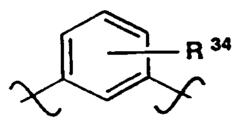
Another embodiment is a compound of formula IV:



(IV)

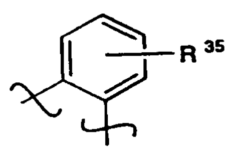
wherein R^{21} is H, NH_2, NHR^{28}, or $NR^{28}R^{29}$, wherein each R^{28} and R^{29}, independently, is C_{1-6} alkyl, C_{1-6} acyl, or C_{2-12} alkyloxycarbonyl; R^{22} is H, C_{1-8} alkyl, (C_{6-40} aryl)-(C_{0-6} alkyl), or (C_{3-10} heteroaryl)(C_{0-6} alkyl); R^{23} is H, C_{1-8} alkyl, or (C_{6-40} aryl)(C_{0-6} alkyl); R^{24} is C_{3-16} cycloalkyl, (C_{6-12} aryl)(C_{0-6} alkyl), (C_{3-16} heterocyclic radical)(C_{0-6} alkyl), (C_{3-10} heteroaryl)-(C_{0-6} alkyl), R^{25}(CH-)(C=O)R^{26}, R^{25}(CH-)(C=S)R^{26}, R^{25}(CH-)(CH_2)R^{26}, or R^{25}(CH_2-), wherein R^{25} is C_{1-6} alkyl, (C_{6-12} aryl)(C_{0-6} alkyl), (C_{3-10} heterocyclic radical)-(C_{0-6} alkyl), (C_{3-10} heteroaryl)(C_{0-6} alkyl), hydroxymethyl, $-(CH_2)_n-A^4-(CH_2)_m-CH_3$, $-(CH_2)_n(C{=}O)NH_2$, or $-(CH_2)_n(C{=}O)NH-(CH_2)_mCH_3$ (wherein A^4 is O, S, SO, or SO_2, n is 0, 1, 2 or 3, and m is 0, 1, or 2), or any other side chain of a naturally occurring amino acid; and R^{26} is H, NH_2, NHOH, C_{3-16} heterocyclic radical, C_{3-16} heteroaryl, NHR^{30}, $NR^{30}R^{31}$, OR^{32}, $NR^{30}OR^{33}$, or $NHOR^{33}$, wherein each of R^{30} and R^{31}, independently, is C_{1-6} alkyl, (C_{6-12} aryl)(C_{0-6} alkyl), (C_{3-16} heterocyclic radical)(C_{0-6} alkyl), (C_{3-16} heteroaryl)(C_{0-6} alkyl), C_{2-14} alkyloxycarbonyl, or where R^{24} is R^{25}(CH-)(CH_2)R^{26}, any amino-protecting group, R^{32} is H, C_{1-6} alkyl, (C_{1-12} acyl)oxy(C_{1-12} alkyl), or (C_{1-12} alkyl)oxy(C_{1-12} alkyl), and R^{33} is H, C_{1-6} alkyl, or (C_{6-40} aryl)(C_{0-6} alkyl); X^4 is =O, =S, or two singly-bonded H;

Y^4 is selected from the following five formulae:



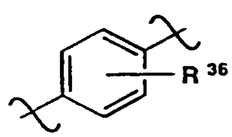
(vi)

wherein R^{34} is H, halide, hydroxy, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-12} alkoxy, C_{1-6} acyloxy, C_{1-6} acyl, C_{6-41} aryl, C_{3-40} heterocyclic radical, C_{3-40} heteroaryl, C_{1-12} alkylsulfonyloxy, C_{1-12} haloalkylsulfonyloxy, C_{6-40} arylsulfonyloxy, or C_{6-41} aryloxy;



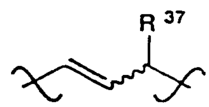
(vii)

wherein R^{35} is H, halide, hydroxy, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-12} alkoxy, C_{1-6} acyloxy, C_{1-6} acyl, C_{6-41} aryl, C_{3-40} heterocyclic radical, C_{3-40} heteroaryl, C_{1-12} alkylsulfonyloxy, C_{1-12} haloalkylsulfonyloxy, C_{6-40} arylsulfonyloxy, or C_{6-41} aryloxy;



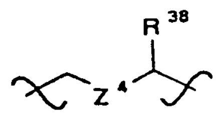
(viii)

wherein R^{36} is H, halide, hydroxy, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-12} alkoxy, C_{1-6} acyloxy, C_{1-6} acyl, C_{6-41} aryl, C_{3-40} heterocyclic radical, C_{3-40} heteroaryl, C_{1-12} alkylsulfonyloxy, C_{1-12} haloalkylsulfonyloxy, C_{6-40} arylsulfonyloxy, or C_{6-41} aryloxy;



(ix)

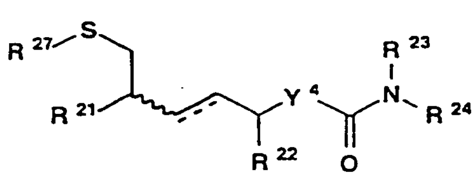
wherein R^{37} is H, C_{1-8} alkyl, (C_{6-40} aryl)(C_{0-6} alkyl), or (C_{3-10} heteroaryl)(C_{0-6} alkyl), (C_{3-10} heterocyclic radical) (C_{0-6} alkyl); and



(x)

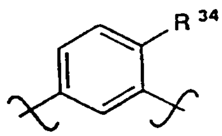
wherein R^{38} is H, C_{1-8} alkyl, (C_{6-40} aryl)(C_{0-6} alkyl), (C_{3-10} heterocyclic radical)(C_{0-6} alkyl), or (C_{3-10} heteroaryl)(C_{0-6} alkyl); and Z^4 is O, S, SO, SO_2, or NR^{39} wherein R^{39} is H, C_{1-6} alkyl, C_{1-6} acyl, (C_{6-40} aryl)-(C_{0-6} alkyl), (C_{3-12} heterocyclic radical)(C_{0-6} alkyl), (C_{3-10} heteroaryl)(C_{0-6} alkyl), or C_{2-14} alkyloxycarbonyl; or wherein R^{38} and NR^{39} taken together form a bifunctional C_{6-40} aryl, a bifunctional C_{3-12} heterocyclic radical, or a bifunctional C_{3-12} heteroaryl; and R^{27} is H; a thiol protecting group; or a moiety set forth in the above generic formula (IV) wherein R^{27} is deleted, said compound being a symmetrical disulfide dimer or an asymmetrical disulfide; or a pharmaceutically acceptable salt thereof.

Another embodiment of the invention is a compound of formula V:

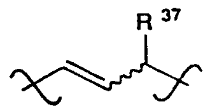


(V)

wherein R^{21} is H, NH_2, or NHR^{28}, wherein R^{28} is C_{1-6} alkyl, C_{1-6} acyl, or C_{2-14} alkyloxycarbonyl; R^{23} is H or methyl; R^{24} is $R^{25}(CH-)(C{=}O)R^{26}$, $R^{25}(CH-)(C{=}S)R^{26}$, or $R^{25}(CH_2-)$; and Y^4 is selected from the following three formulae:

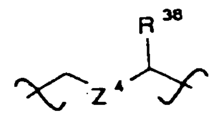


(xi)



(xii)

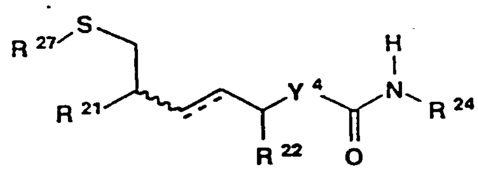
and



(xiii)

wherein Z^4 is O, S, or NR^{39}, wherein R^{39} is H, C_{1-6} alkyl, or C_{1-6} acyl; or wherein R^{38} and NR^{39} taken together form a bifunctional C_{6-40} aryl, a bifunctional C_{3-12} heterocyclic radical, or a bifunctional C_{3-12} heteroaryl.

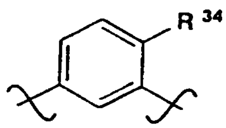
Another embodiment is a compound of formula VI:



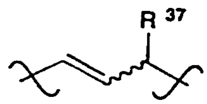
(VI)

wherein R^{21} is NH_2 or NHR^{28}, wherein R^{28} is C_{1-6} alkyl, C_{1-6} acyl, or C_{2-14} alkyloxycarbonyl; R^{22} is H or C_{1-8} alkyl; R^{24} is C_{3-16} heterocyclic radical, C_{3-16} heteroaryl, $R^{25}(CH-)(C{=}O)R^{26}$, or $R^{25}(CH-)(C{=}S)R^{26}$, wherein R^{25} is C_{1-6} alkyl, hydroxymethyl, $-(CH_2)_n-A^4-(CH_2)_m-CH_3$, $-(CH_2)_n(C{=}O)NH_2$, or $-(CH_2)_n(C{=}O)NH(CH_2)_mCH_3$ (wherein A^4 is O, S, SO, or SO_2, n is 0, 1, or 2, and m is 0 or 1), or any other side chain of a naturally occurring amino acid, and R^{32} is H, C_{1-6} alkyl, or (C_{1-12} acyl)oxy(C_{1-12} alkyl); and

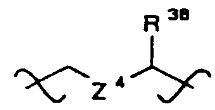
Y^4 is selected from the following three formulae:



(xiv)



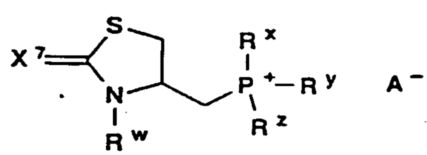
(xv) and



(xvi)

wherein Z^4 is O, S, or NR^{39}, wherein R^{39} is H, C_{1-6} alkyl, or C_{1-6} acyl; or wherein R^{38} and NR^{39} taken together form a bifunctional C_{6-40} aryl, a bifunctional C_{3-12} heterocyclic radical, or a bifunctional C_{3-12} heteroaryl.

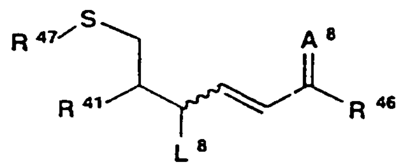
Another embodiment is a compound of formula VII:



(VII)

wherein X^7 is O or S; R^W is H, C_{1-8} alkyl, C_{1-8} acyl, or C_{2-14} alkyloxycarbonyl; each of R^x, R^y, and R^z, independently, is C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{6-20} aryl, (C_{6-20} aryl)(C_{1-12} alkyl), or (C_{1-12} alkyl)(C_{6-20} aryl); and A^- is a counter-ion. In certain embodiments, A^- is bromide, iodide, or chloride; X^7 is O; R^w is H or methyl; and each of R^x, R^y, and R^z, independently, is (C_{6-10} aryl)(C_{0-6} alkyl), and preferably each of R^x, R^y, and R^z is phenyl.

Another embodiment is a compound of formula VIII:

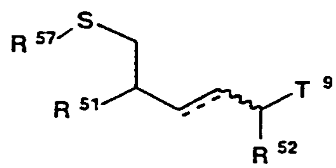


(VIII)

wherein:

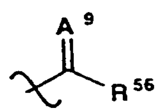
R^{41} is H, NH_2, NHR^{42}, or $NR^{42}R^{43}$, wherein R^{42} is C_{1-6} alkyl, C_{1-6} acyl, C_{2-14} alkyloxycarbonyl, or any other amino-protecting group, and R^{43} is C_{1-6} alkyl, C_{1-6} acyl, C_{2-14} alkyloxycarbonyl or, when taken together with R^{47}, is a bifunctional thiol-protecting group; L^8 is halide, hydroxy, C_{1-12} alkoxy, C_{1-12} alkylsulfonyloxy, C_{6-20} arylsulfonyloxy, C_{1-12} acyloxy, C_{1-12} carbamoyl, or any other activated leaving group; A^8 is =O, =S, or two singly-bonded H; R^{46} is H, NH_2, NHOH, C_{3-10} heterocyclic radical, C_{3-10} heteroaryl, NHR^{44}, $NR^{44}R^{45}$, OR^{48}, $NR^{44}OR^{45}$, $NHOR^{49}$, or any other carboxyl-protecting group, wherein each of R^{44} and R^{45}, independently, is C_{1-6} alkyl, $(C_{6-12}$ aryl$)(C_{0-6}$ alkyl$)$, $(C_{3-16}$ heterocyclic radical$)(C_{0-6}$ alkyl$)$, $(C_{3-16}$ hetero-aryl$)(C_{0-6}$ alkyl$)$, or C_{2-14} alkyloxycarbonyl, R^{48} is H, C_{1-6} alkyl, $(C_{1-12}$ acyl$)$oxy$(C_{1-12}$ alkyl$)$, $(C_{1-12}$ alkyl$)$oxy-$(C_{1-12}$ alkyl$)$, or any other carboxyl- or hydroxyl-protecting group, and R^{49} is H, or C_{1-6} alkyl, provided that where A^8 is two singly-bonded H, R^{46} is such that the C atom bonded to both A^8 and R^{46} is bonded to either a N or O atom of R^{46}; and R^{47} is H; a thiol-protecting group or, when taken together with R^{43}, a bifunctional thiol-protecting group; or a moiety set forth in the above generic formula (VIII) wherein R^{47} is deleted, said compound being a symmetrical disulfide dimer or an asymmetrical disulfide.

Another embodiment is a compound of formula IX:

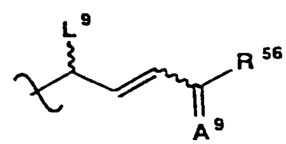


(IX)

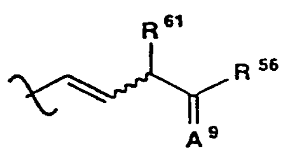
wherein: R^{51} is H, NHR^{53}, or $NR^{53}R^{54}$, wherein R^{53} is H, C_{1-6} alkyl, C_{1-6} acyl, C_{2-14} alkyloxycarbonyl, or any other amino-protecting group, and R^{54} is C_{1-6} alkyl, C_{1-6} acyl, C_{2-14} alkyloxycarbonyl or, when taken together with R^{57}, a bifunctional thiol-protecting group; R^{52} is H, C_{1-8} alkyl, (C_{6-40} aryl)(C_{0-6} alkyl), or (C_{3-10} heteroaryl)(C_{0-6} alkyl); T^9 is selected from the following four formulae:



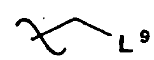
(xvii)



(xviii)



(xix) and

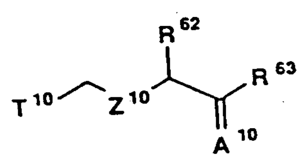


(xx)

wherein L^9 is halide, hydroxy, C_{1-12} alkoxy, C_{1-12} alkylsulfonyloxy, C_{6-20} arylsulfonyloxy, C_{1-12} acyloxy, C_{1-12} carbamoyl, or any other activated leaving group; A^9 is =O, =S, or two singly-bonded H; R^{56} is H, NH_2, NHOH, C_{3-10} heterocyclic radical, C_{3-10} heteroaryl, NHR^{55}, $NR^{55}R^{58}$, OR^{59}, $NR^{55}OR^{58}$, $NHOR^{60}$, or any other carboxyl-protecting group, wherein each R^{55} and R^{58}, independently, is C_{1-6} alkyl, (C_{6-12} aryl)(C_{0-6} alkyl),

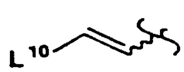
(C_{3-16} heterocyclic radical)(C_{0-6} alkyl), (C_{3-16} heteroaryl)-(C_{0-6} alkyl), or C_{2-14} alkyloxycarbonyl, R^{59} is H, C_{1-6} alkyl, (C_{1-12} acyl)oxy(C_{1-12} alkyl), or (C_{1-12} alkyl)oxy-(C_{1-12} alkyl), and R^{60} is H or C_{1-6} alkyl; provided that where A^9 is two singly-bonded H, R^{56} is selected such that the carbon atom bonded to both A^9 and R^{56} is bonded to either a nitrogen or oxygen atom of R^{56}; R^{61} is H, C_{1-8} alkyl, (C_{6-40} aryl)(C_{0-6} alkyl), or (C_{3-10} heteroaryl)-(C_{0-6} alkyl); and R^{57} is H; a thiol-protecting group or, taken together with R^{54}, a bifunctional thiol-protecting group; or a moiety set forth in the above generic formula (IX) wherein R^{57} is deleted, said compound being a symmetrical disulfide dimer or an asymmetrical disulfide.

Another embodiment is a compound of formula X:

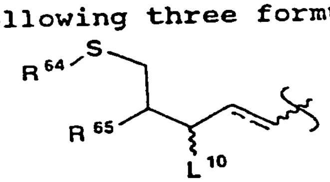


(X)

wherein: T^{10} is selected from the following three formulae:

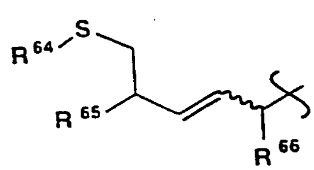


(xxi)



(xxii)

and

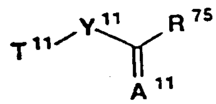


(xxiii)

wherein L^{10} is halide, C_{1-12} alkoxy, C_{1-12} alkylsulfonyloxy,

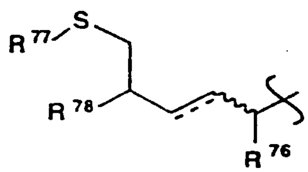
C_{6-20} arylsulfonyloxy, C_{1-12} acyloxy, C_{1-12} carbamoyl, or any other activated leaving group; R^{65} is H, NH_2, NHR^{67}, or $NR^{67}R^{68}$, wherein R^{67} is C_{1-6} alkyl, C_{1-6} acyl, C_{2-14} alkyloxycarbonyl or any other amino-protecting group, and R^{68} is C_{1-6} alkyl, C_{1-6} acyl, C_{2-14} alkyloxycarbonyl or, when taken together with R^{64}, a bifunctional thiol-protecting group; R^{64} is H; a thiol-protecting group or, when taken together with R^{68}, a bifunctional thiol-protecting group; or a moiety set forth in the above generic formula (X) wherein R^{64} is deleted, said compound being a symmetrical disulfide dimer or an asymmetrical disulfide; R^{66} is H, C_{1-8} alkyl, (C_{6-40} aryl)(C_{0-6} alkyl), or C_{3-10} heteroaryl)(C_{0-6} alkyl); R^{63} is H, NH_2, NHOH, C_{3-10} heterocyclic radical, C_{3-10} heteroaryl, NHR^{69}, $NR^{69}R^{70}$, OR^{71}, $NR^{69}OR^{70}$, $NHOR^{72}$, or any other carboxyl-protecting group, wherein each of R^{69} and R^{70}, independently, is C_{1-6} alkyl, (C_{3-16} heterocyclic radical)(C_{0-6} alkyl), or (C_{3-16} heteroaryl)(C_{0-6} alkyl), R^{71} is H, C_{1-6} alkyl, (C_{1-12} acyl)oxy(C_{1-12} alkyl), or (C_{1-12} alkyl)oxy(C_{1-12} alkyl), and R^{72} is H or C_{1-6} alkyl; provided that where A^{10} is two singly-bonded H, R^{63} is selected such that the carbon atom bonded to both A^{10} and R^{63} is bonded to either a nitrogen or oxygen atom of R^{63}; A^{10} is O, S, or two singly-bonded H; and R^{62} is H, C_{1-8} alkyl, (C_{6-40} aryl)(C_{0-6} alkyl), (C_{3-10} heterocyclic radical)(C_{0-6} alkyl), or (C_{3-10} heteroaryl)(C_{0-6} alkyl); and Z^{10} is O, S, SO, SO_2, or NR^{73} wherein R^{73} is H, C_{1-6} alkyl, C_{1-6} acyl, (C_{6-40} aryl)(C_{0-6} alkyl), (C_{3-10} heteroaryl)-(C_{0-6} alkyl), or C_{2-14} alkyloxycarbonyl.

Another embodiment is a compound of formula XI:



(XI)

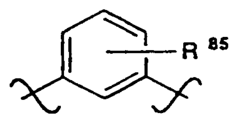
wherein: T^{11} is selected from H-(C=O)-, H-(C=O)-CH(R^{76})-,



(xxiv) and (xxv)

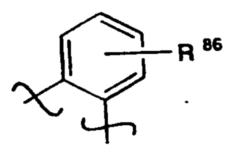
wherein R^{75} is H, NH_2, NHOH, C_{3-16} heterocyclic radical, C_{3-16} heteroaryl, NHR^{81}, $NR^{81}R^{82}$, OR^{83}, $NR^{81}OR^{82}$, $NHOR^{84}$ or any other carboxyl-protecting group, wherein each R^{81} and R^{82}, independently, is C_{1-6} alkyl, (C_{6-12} aryl)(C_{0-6} alkyl), (C_{3-16} heterocyclic radical)(C_{0-6} alkyl), or (C_{3-16} heteroaryl)(C_{0-6} alkyl), R^{83} is H, C_{1-6} alkyl, (C_{1-12} acyl)oxy(C_{1-12} alkyl), or (C_{1-12} alkyl)oxy-(C_{1-12} alkyl), and R^{84} is H, or C_{1-6} alkyl; R^{76} is H, C_{1-8} alkyl, (C_{6-40} aryl)(C_{0-6} alkyl), or (C_{3-10} heteroaryl)(C_{0-6} alkyl); R^{77} is H; a thiol-protecting group or, when taken together with R^{80}, a bifunctional thiol-protecting group; or a moiety set forth in the above generic formula (XI) wherein R^{77} is deleted, said compound being a symmetrical disulfide dimer or an asymmetrical disulfide; R^{78} is H, NH_2, NHR^{79}, or $NR^{79}R^{80}$, wherein R^{79} is C_{1-6} alkyl, C_{1-6} acyl, C_{2-14} alkyloxycarbonyl or any other amino-protecting group, and R^{80} is C_{1-6} alkyl, C_{1-6} acyl,

C_{2-14} alkyloxycarbonyl or, when taken together with R^{77}, a bifunctional thiol-protecting group; L^{11} is halide, C_{1-12} alkylsulfonyloxy, C_{6-20} arylsulfonyloxy, C_{2-12} alkylcarbonyloxy, or any other activated leaving group; Y^{11} is selected from the following three formulae:



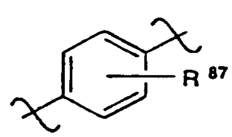
(xxvi)

wherein R^{85} is H, halide, hydroxy, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-12} alkoxy, C_{1-6} acyloxy, C_{1-6} acyl, C_{6-41} aryl, C_{3-40} heterocyclic radical, C_{3-40} heteroaryl, C_{1-12} alkylsulfonyloxy, C_{1-12} haloalkylsulfonyloxy, C_{6-40} arylsulfonyloxy, or C_{6-41} aryloxy;



(xxvii)

wherein R^{86} is H, halide, hydroxy, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-12} alkoxy, C_{1-6} acyloxy, C_{1-6} acyl, C_{6-41} aryl, C_{3-40} heterocyclic radical, C_{3-40} heteroaryl, C_{1-12} alkylsulfonyloxy, C_{1-12} haloalkylsulfonyloxy, C_{6-40} arylsulfonyloxy, or C_{6-41} aryloxy; and



(xxviii)

wherein R^{87} is H, halide, hydroxy, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-12} alkoxy, C_{1-6} acyloxy, C_{1-6} acyl, C_{6-41} aryl, C_{3-40} heterocyclic radical, C_{3-40} heteroaryl,

C_{1-12} alkylsulfonyloxy, C_{1-12} haloalkylsulfonyloxy, C_{6-40} arylsulfonyloxy, or C_{6-41} aryloxy; and A^{11} is O, S, or two singly-bonded H.

Another embodiment is a compound of formula VIII, wherein R^{41} is H, NH_2, NHR^{42}, or $NR^{42}R^{43}$, wherein R^{42} is C_{1-6} alkyl, C_{1-6} acyl, C_{2-14} alkyloxycarbonyl, or any other amino-protecting group, and R^{43} is C_{1-6} alkyl, C_{1-6} acyl, C_{2-14} alkyloxycarbonyl or, when taken together with R^{47}, is a bifunctional thiol-protecting group; L^8 is halide, hydroxy, C_{1-7} alkoxy, C_{1-7} alkylsulfonyloxy, C_{6-12} arylsulfonyloxy, C_{1-12} acyloxy, C_{1-12} carbamoyl, or any other activated leaving group; A^8 is =O, =S, or two singly-bonded H; R^{46} is H, NH_2, NHOH, C_{3-10} heterocyclic radical, C_{3-10} heteroaryl, NHR^{44}, $NR^{44}R^{45}$, OR^{48}, $NR^{44}OR^{45}$, $NHOR^{49}$, or any other carboxyl-protecting group, wherein each of R^{44} and R^{45}, independently, is C_{1-6} alkyl, $(C_{6-10}$ aryl$)(C_{0-3}$ alkyl$)$, $(C_{3-10}$ heterocyclic radical$)(C_{0-3}$ alkyl$)$, or $(C_{3-10}$ hetero-aryl$)(C_{0-3}$ alkyl$)$, R^{48} is H, C_{1-6} alkyl, $(C_{1-7}$ acyl$)$oxy-$(C_{1-6}$ alkyl$)$, $(C_{1-6}$ alkyl$)$oxy$(C_{1-6}$ alkyl$)$, or any other carboxyl- or hydroxyl-protecting group, and R^{49} is H, or C_{1-6} alkyl, provided that where A^8 is two singly-bonded H, R^{46} is such that the C atom bonded to both A^8 and R^{46} is bonded to either a N or O atom of R^{46}; and R^{47} is H; a thiol-protecting group or, when taken together with R^{43}, a bifunctional thiol-protecting group; or a moiety set forth in the above formula (VIII) wherein R^{47} is deleted, said compound being a symmetrical disulfide dimer or an asymmetrical disulfide.

Another embodiment is a compound of formula IX, wherein R^{51} is H, NHR^{53}, or $NR^{53}R^{54}$, wherein R^{53} is H, C_{1-6} alkyl, C_{1-6} acyl, C_{2-14} alkyloxycarbonyl, or any other amino-protecting group, and R^{54} is C_{1-6} alkyl, C_{1-6} acyl,

C_{2-14} alkyloxycarbonyl or, when taken together with R^{57}, a bifunctional thiol-protecting group; R^{52} is H, C_{1-8} alkyl, (C_{6-10} aryl)(C_{0-3} alkyl), or (C_{3-10} heteroaryl)(C_{0-3} alkyl); wherein L^9 is halide, hydroxy, C_{1-7} alkoxy, C_{1-6} alkylsulfonyloxy, C_{6-10} arylsulfonyloxy, C_{1-7} acyloxy, C_{1-7} carbamoyl,or any other activated leaving group; A^9 is =O, =S, or two singly-bonded H; R^{56} is H, NH_2, NHOH, C_{3-8} heterocyclic radical, C_{3-8} heteroaryl, NHR^{55}, $NR^{55}R^{58}$, OR^{59}, $NR^{55}OR^{58}$, $NHOR^{60}$, or any other carboxyl-protecting group, wherein each R^{55} and R^{58}, independently, is C_{1-6} alkyl, (C_{6-10} aryl)(C_{0-3} alkyl), (C_{3-10} heterocyclic radical)(C_{0-3} alkyl), or (C_{3-10} heteroaryl)(C_{0-3} alkyl), R^{59} is H, C_{1-6} alkyl, (C_{1-7} acyl)oxy(C_{1-7} alkyl), or (C_{1-7} alkyl)-oxy(C_{1-7} alkyl), and R^{60} is H or C_{1-6} alkyl; provided that where A^9 is two singly-bonded H, R^{56} is selected such that the carbon atom bonded to both A^9 and R^{56} is bonded to either a nitrogen or oxygen atom of R^{56}; and R^{61} is H, C_{1-8} alkyl, (C_{6-20} aryl)-(C_{0-3} alkyl), or (C_{3-10} heteroaryl)-(C_{0-3} alkyl); R^{57} is H; a thiol-protecting group or, taken together with R^{54}, a bifunctional thiol-protecting group; or a moiety set forth in the above formula (IX) wherein R^{57} is deleted, said compound being a symmetrical disulfide dimer.

Another embodiment is a compound of formula X, wherein L^{10} is halide, C_{1-7} alkoxy, C_{1-7} alkylsulfonyloxy, C_{6-10} arylsulfonyloxy, C_{1-7} acyloxy, C_{1-7} carbamoyl, or any other activated leaving group; R^{65} is H, NH_2, NHR^{67}, or $NR^{67}R^{68}$, wherein R^{67} is C_{1-6} alkyl, C_{1-6} acyl, C_{2-14} alkyloxycarbonyl or any other amino-protecting group, and R^{68} is C_{1-6} alkyl, C_{1-6} acyl, C_{2-14} alkyloxycarbonyl or, when taken together with R^{64}, a bifunctional thiol-protecting group; R^{64} is H; a thiol-protecting group or, when taken together with R^{68}, a bifunctional thiol-protecting group; or a moiety set forth in the above generic formula (X) wherein R^{64} is

deleted, said compound being a symmetrical disulfide dimer or an asymmetrical disulfide; R^{66} is H, C_{1-8} alkyl, $(C_{6-20}$ aryl)$(C_{0-3}$ alkyl), or $(C_{3-10}$ heteroaryl)$(C_{0-3}$ alkyl); R^{63} is H, NH_2, NHOH, C_{3-10} heterocyclic radical, C_{3-10} heteroaryl, NHR^{69}, $NR^{69}R^{70}$, OR^{71}, $NR^{69}OR^{70}$, $NHOR^{72}$, or any other carboxyl-protecting group, wherein each of R^{69} and R^{70}, independently, is C_{1-6} alkyl, $(C_{3-10}$ heterocyclic radical)$(C_{0-3}$ alkyl), or $(C_{3-10}$ heteroaryl)$(C_{0-3}$ alkyl), R^{71} is H, C_{1-6} alkyl, $(C_{1-7}$ acyl)oxy$(C_{1-6}$ alkyl), or $(C_{1-6}$ alkyl)oxy$(C_{1-6}$ alkyl), and R^{72} is H or C_{1-6} alkyl; provided that where A^{10} is two singly-bonded H, R^{63} is selected such that the carbon atom bonded to both A^{10} and R^{63} is bonded to either a nitrogen or oxygen atom of R^{63}; and R^{62} is H, C_{1-8} alkyl, $(C_{6-20}$ aryl)$(C_{0-3}$ alkyl), $(C_{3-10}$ heterocyclic radical)$(C_{0-3}$ alkyl), or $(C_{3-10}$ heteroaryl)$(C_{0-3}$ alkyl); and Z^{10} is O, S, SO, SO_2, or NR^{73} wherein R^{73} is H, C_{1-6} alkyl, C_{1-6} acyl, $(C_{6-20}$ aryl)-$(C_{0-3}$ alkyl), $(C_{3-10}$ heteroaryl)$(C_{0-3}$ alkyl), or C_{2-14} alkyloxycarbonyl.

Another embodiment is a compound of formula XI, wherein: R^{75} is H, NH_2, NHOH, C_{3-10} heterocyclic radical, C_{3-10} heteroaryl, NHR^{81}, $NR^{81}R^{82}$, OR^{83}, $NR^{81}OR^{82}$, $NHOR^{84}$ or any other carboxyl-protecting group, wherein each R^{81} and R^{82}, independently, is C_{1-6} alkyl, $(C_{6-10}$ aryl)$(C_{0-3}$ alkyl), $(C_{3-10}$ heterocyclic radical)$(C_{0-3}$ alkyl), or $(C_{3-10}$ heteroaryl)$(C_{0-3}$ alkyl), R^{83} is H, C_{1-6} alkyl, $(C_{3-10}$ heteroaryl)$(C_{0-3}$ alkyl), $(C_{1-7}$ acyl)oxy$(C_{1-6}$ alkyl), or $(C_{1-6}$ alkyl)oxy$(C_{1-6}$ alkyl), and R^{84} is H, or C_{1-6} alkyl; R^{76} is H, C_{1-8} alkyl, $(C_{6-20}$ aryl)$(C_{0-3}$ alkyl), or $(C_{3-10}$ heteroaryl)$(C_{0-3}$ alkyl); R^{77} is H; a thiol-protecting group or, when taken together with R^{80}, a bifunctional thiol-protecting group; or a moiety set forth in the above formula (XI) wherein R^{77} is deleted, said compound being a symmetrical disulfide dimer; R^{78} is H,

NH_2, NHR^{79}, or $NR^{79}R^{80}$, wherein R^{79} is C_{1-6} alkyl, C_{1-6} acyl, C_{2-14} alkyloxycarbonyl or any other amino-protecting group, and R^{80} is C_{1-6} alkyl, C_{1-6} acyl, C_{2-14} alkyloxycarbonyl or, when taken together with R^{77}, a bifunctional thiol-protecting group; L^{11} is halide, C_{1-6} alkoxy, C_{1-6} alkylsulfonyloxy, C_{6-10} arylsulfonyloxy, C_{1-7} acyloxy, C_{1-7} carbamoyl, or any other activated leaving group; and R^{85} is H, halide, hydroxy, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-7} alkoxy, C_{1-6} acyloxy, C_{1-6} acyl, C_{6-20} aryl, C_{3-16} heterocyclic radical, C_{3-16} heteroaryl, C_{1-6} alkylsulfonyloxy, C_{1-6} haloalkylsulfonyloxy, C_{6-20} arylsulfonyloxy, or C_{6-20} aryloxy.

Where any of the terms *any other amino-protecting group*, *any other hydroxyl-protecting group*, *any other carboxyl-protecting group*, or *any other thiol-protecting group*, is used, the term applies only where the designated amino, hydroxyl, carboxyl, or thiol group is evident. For example in formula (I), where R^4 is $R^5(CH-)(C{=}O)R^6$, and R^6 is OR^{12}, R^{12} can be a C_{1-6} alkyl (to form an ester) or R^{12} can be any other carboxyl-protecting group. Where R^4 is $R^5(CH-)(CH_2)R^6$, a carboxyl group is not possible, although if R^6 is $NR^{10}OR^{11}$, then R^{10} can be an amino-protecting group.

This invention is based, in part, on the structure-function data disclosed herein. Therefore another aspect of the invention encompasses any compound, including metabolic precursors of the inhibitor compounds of the invention, that contains an essential recognition moiety and an essential inhibitory moiety as disclosed herein. These essential moieties may also be in a masked form which is released by metabolic or other processes after administration to a patient. When metabolized or unmasked, these compounds inhibit the post-translational processing of ras proteins by FTase, GGTase, or both.

D. Synthesis

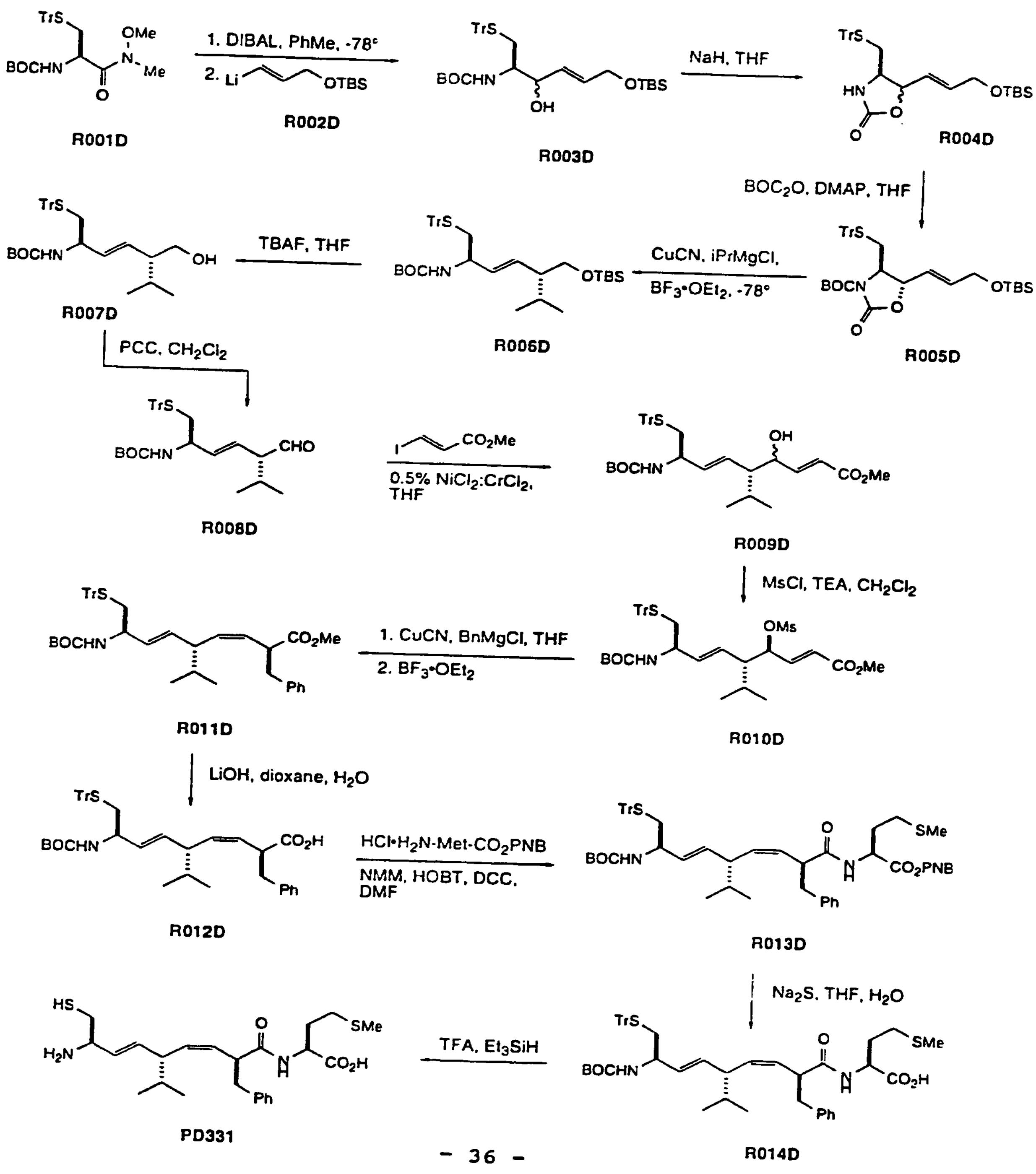
The invention also relates to methods of making the compounds disclosed herein. Schemes I-XI are synthetic pathways that have been used to make compounds PD331; PD331; R030D; PA041; PA091; PE021; PT011; PM061; R012M; PM031 and PM121; and R031M, respectively. These synthetic pathways can easily be modified by an organic chemist of ordinary skill to make the other related compounds disclosed herein.

One aspect of this invention is a method of making the disclosed compounds via any of the disclosed intermediates. These intermediates include synthetic intermediates (e.g., R007D, R011D, R019D, R020D, R023D, R029D, R003E, R005E, R004T, R003M - R006M, R017M, R025M, and R027M); partially-protected therapeutic compounds (e.g., R006A, R004A, R003A, R012A, R014D, and R023M); fully-protected therapeutic compounds (e.g., R024D, R007E, R001A, R007T, R013D, and R018M); and the disclosed Wittig reagents (e.g., R012M). The intermediates and inhibitor compounds of the invention can also be made by other methods known or easily developed by those in the art.

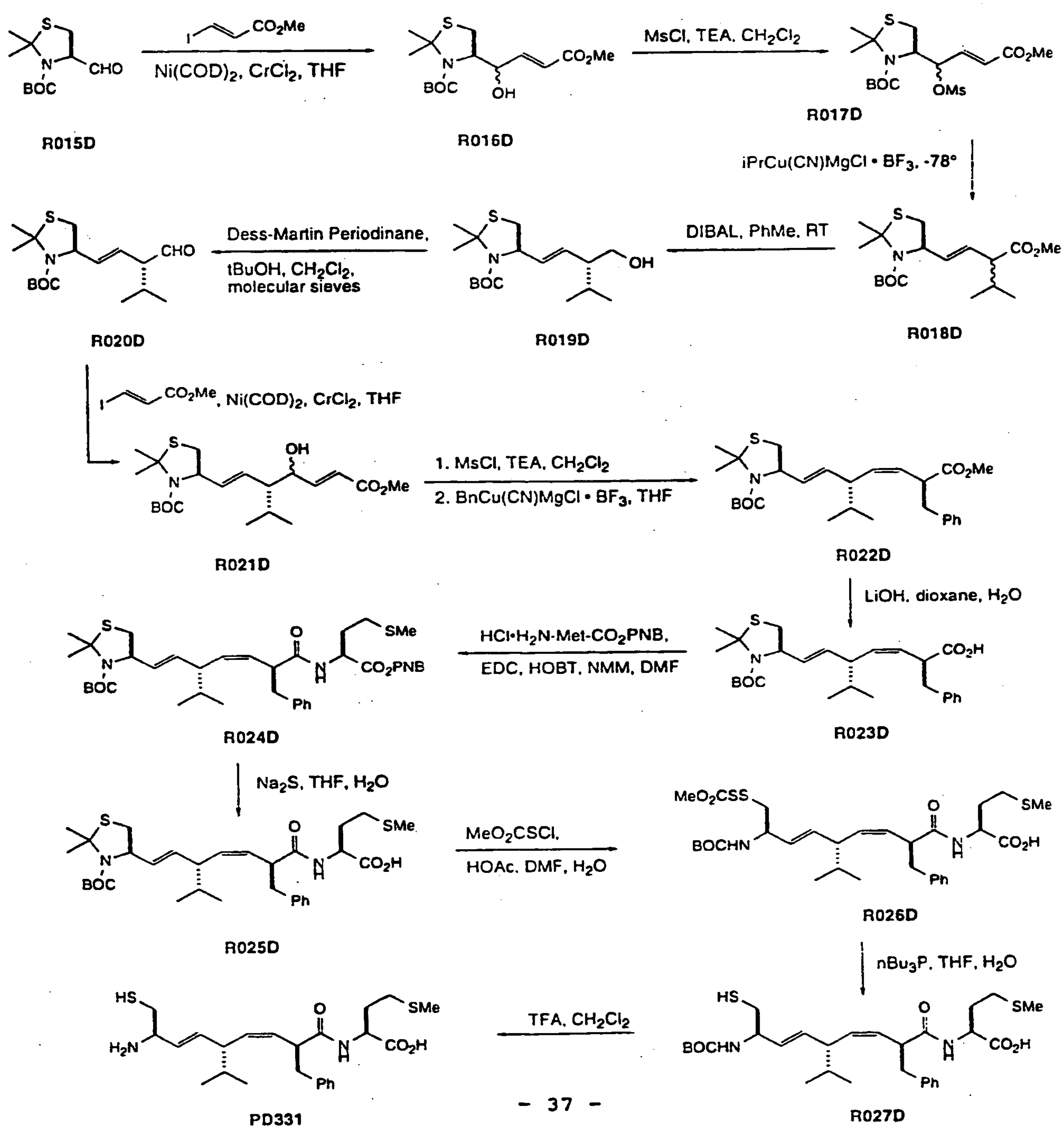
In another aspect of the invention, the intermediates disclosed herein (e.g., Wittig reagent R012M and related compounds) are used in a method of making compounds (particularly but not limited to inhibitors of isoprenyl transferases) which are not disclosed herein.

Synthetic experimental details and/or 400 MHz ^{1}H NMR data are provided below in Examples 1-175 for over 95 inhibitor compounds which have been prepared. The number of inhibitor compounds does not include the many corresponding partially- and fully-protected intermediate compounds of the invention.

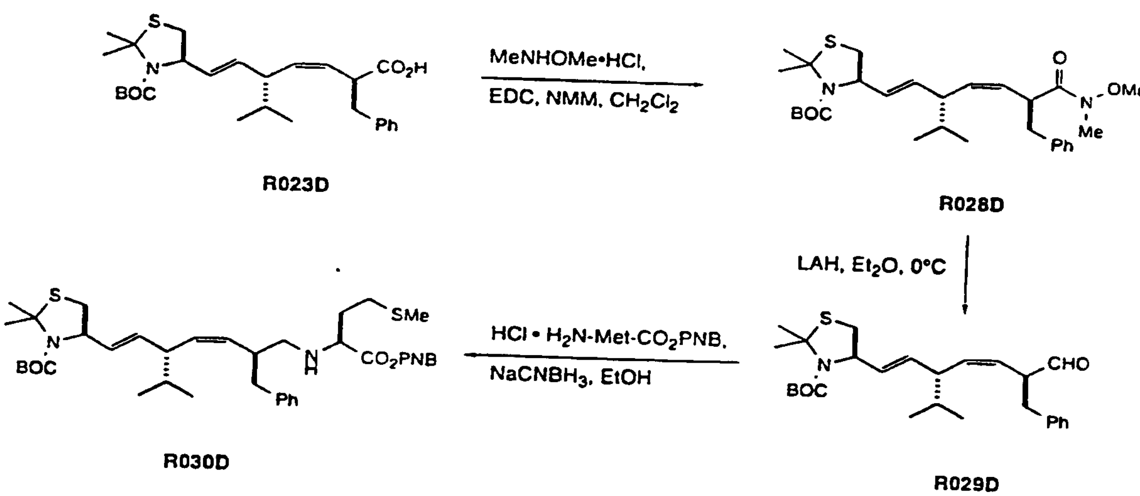
Scheme I


R001D
R002D
R003D
R004D
R005D
R006D
R007D
R008D
R009D
R010D
R011D
R012D
R013D
R014D
PD331
1. DIBAL, PhMe, -78°
2. Li OTBS
NaH, THF
BOC2O, DMAP, THF
CuCN, iPrMgCl, BF3•OEt2, -78°
TBAF, THF
PCC, CH2Cl2
CO2Me
0.5% NiCl2:CrCl2, THF
MsCl, TEA, CH2Cl2
1. CuCN, BnMgCl, THF
2. BF3•OEt2
LiOH, dioxane, H2O
HCl•H2N-Met-CO2PNB
NMM, HOBT, DCC, DMF
Na2S, THF, H2O
TFA, Et3SiH

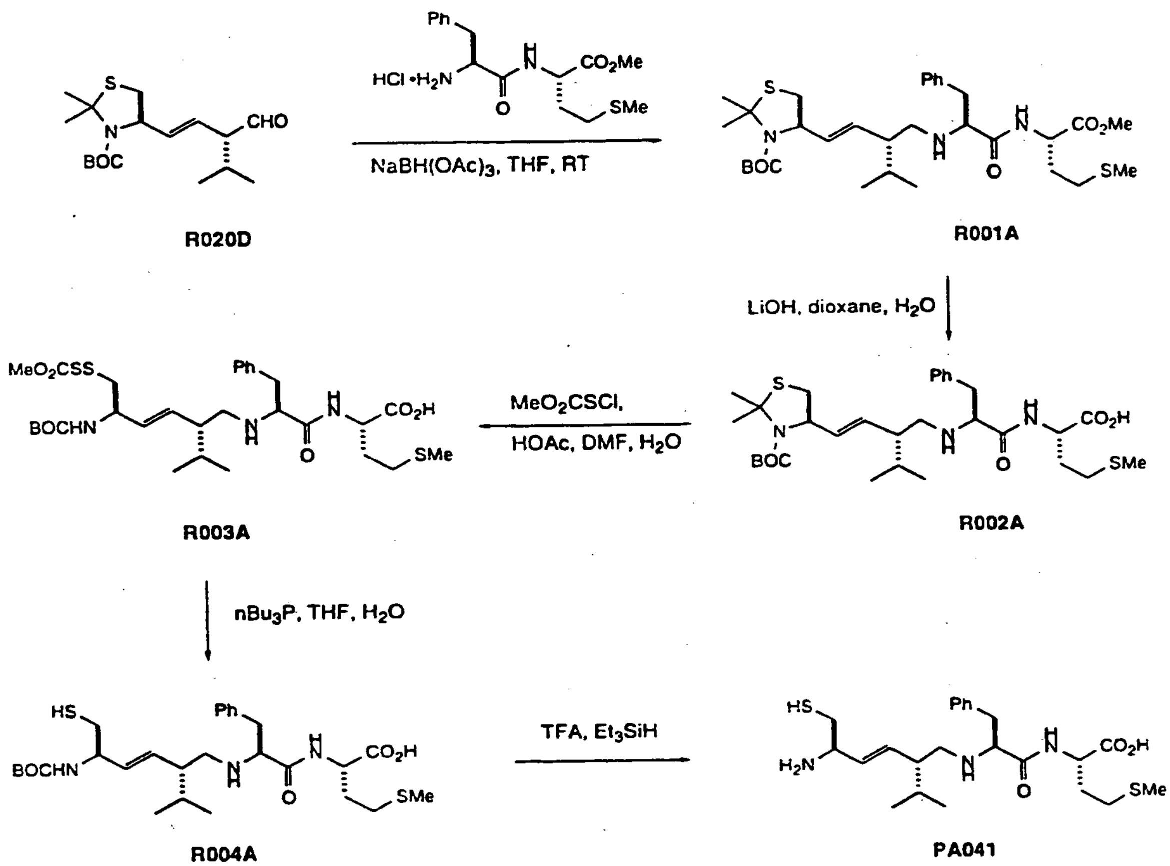
Scheme II


CO2Me
Ni(COD)2, CrCl2, THF
R015D
R016D
MsCl, TEA, CH2Cl2
R017D
iPrCu(CN)MgCl • BF3, -78°
R018D
DIBAL, PhMe, RT
R019D
Dess-Martin Periodinane,
tBuOH, CH2Cl2,
molecular sieves
R020D
CO2Me, Ni(COD)2, CrCl2, THF
R021D
1. MsCl, TEA, CH2Cl2
2. BnCu(CN)MgCl • BF3, THF
R022D
LiOH, dioxane, H2O
R023D
HCl•H2N-Met-CO2PNB,
EDC, HOBT, NMM, DMF
R024D
Na2S, THF, H2O
R025D
MeO2CSCl,
HOAc, DMF, H2O
R026D
nBu3P, THF, H2O
R027D
TFA, CH2Cl2
PD331

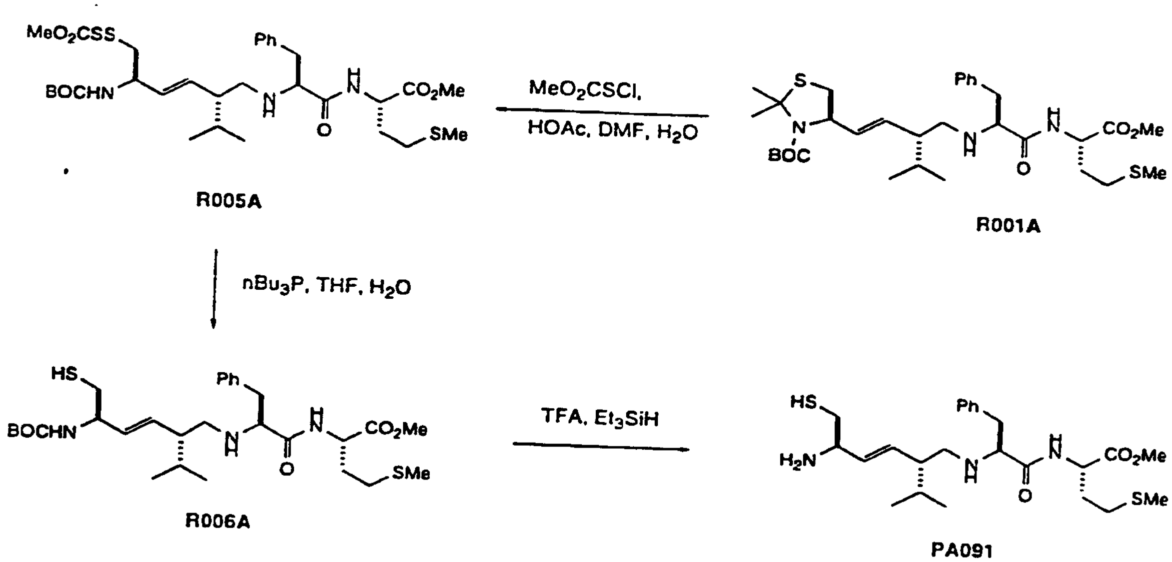
Scheme III


MeNHOMe•HCl,
EDC, NMM, CH_2Cl_2
LAH, Et_2O, 0°C
HCl • H_2N-Met-CO_2PNB,
$NaCNBH_3$, EtOH
R023D
R028D
R029D
R030D

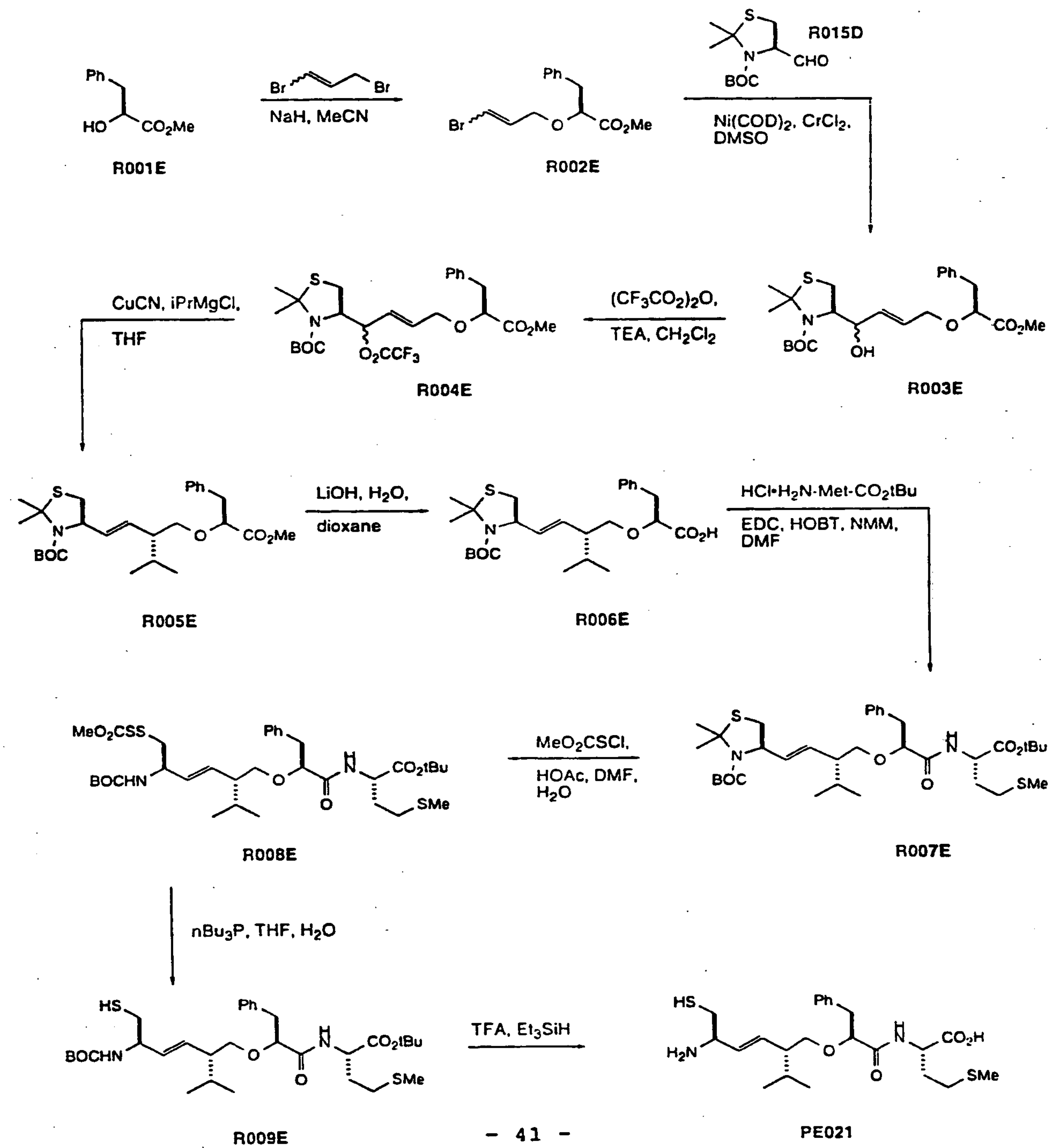
Scheme IV


HCl•H2N
Ph
CO2Me
SMe
NaBH(OAc)3, THF, RT
BOC
CHO
R020D
R001A
LiOH, dioxane, H2O
MeO2CSS
BOCHN
CO2H
MeO2CSCl,
HOAc, DMF, H2O
R003A
R002A
nBu3P, THF, H2O
HS
TFA, Et3SiH
H2N
R004A
PA041

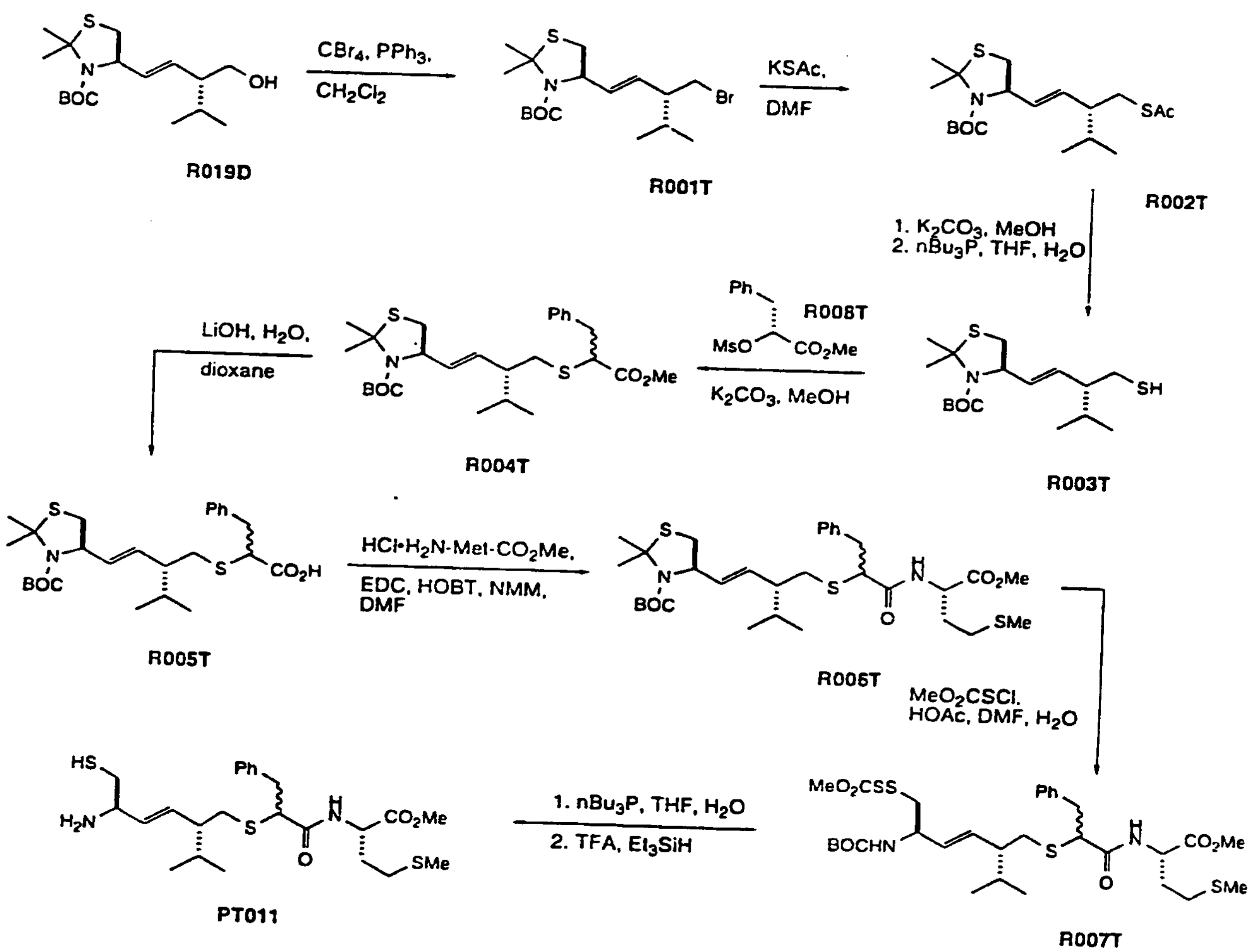
Scheme V


MeO2CSS
BOCHN
Ph
CO2Me
SMe
R005A
MeO2CSCl,
HOAc, DMF, H2O
S
N
BOC
R001A
nBu3P, THF, H2O
HS
R006A
TFA, Et3SiH
H2N
PA091

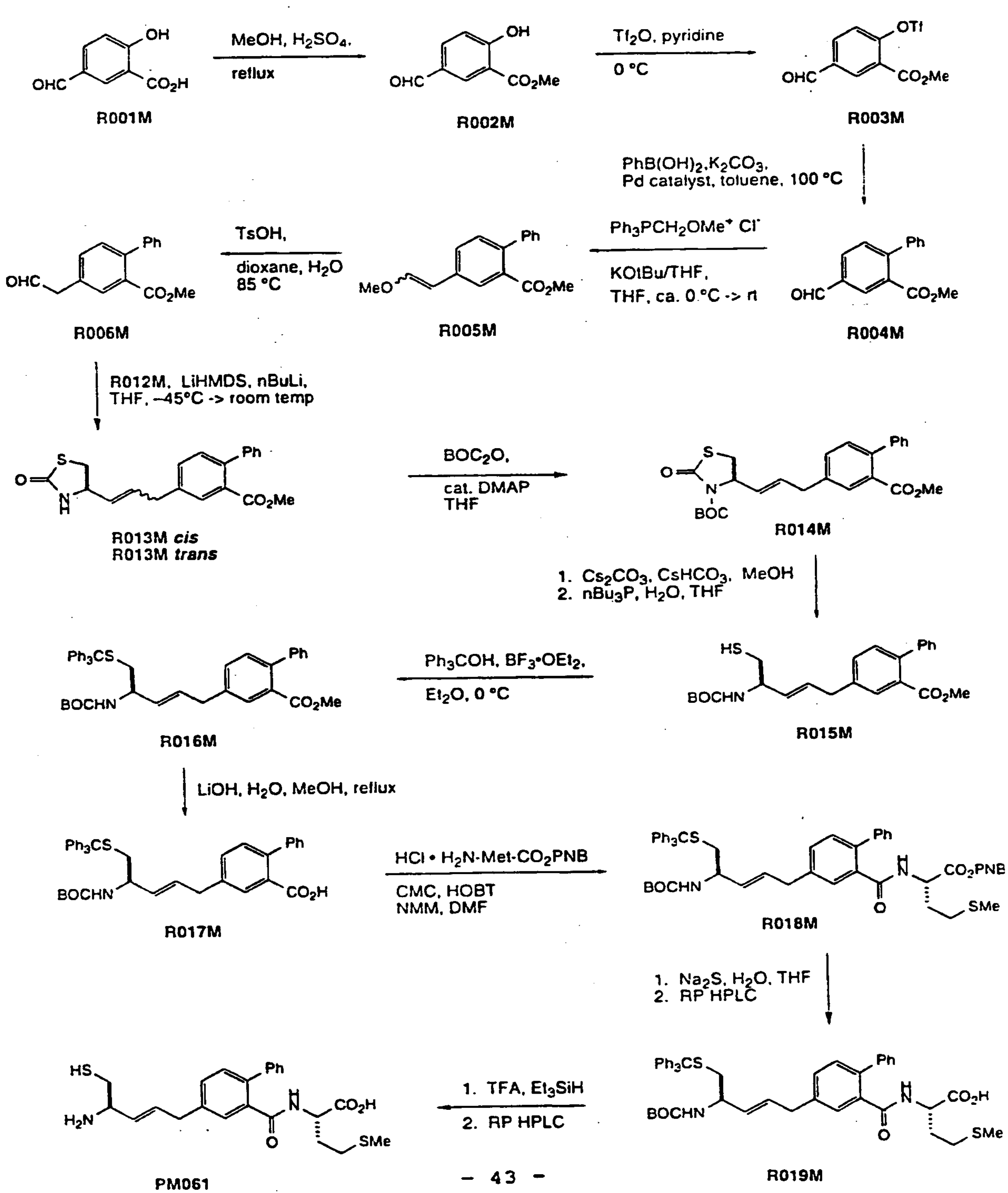
Scheme VI


R015D
NaH, MeCN
Ni(COD)2, CrCl2, DMSO
R001E
R002E
CuCN, iPrMgCl, THF
(CF3CO2)2O, TEA, CH2Cl2
R004E
R003E
LiOH, H2O, dioxane
HCl•H2N-Met-CO2tBu
EDC, HOBT, NMM, DMF
R005E
R006E
MeO2CSCl, HOAc, DMF, H2O
R008E
R007E
nBu3P, THF, H2O
TFA, Et3SiH
R009E
PE021

Scheme VII

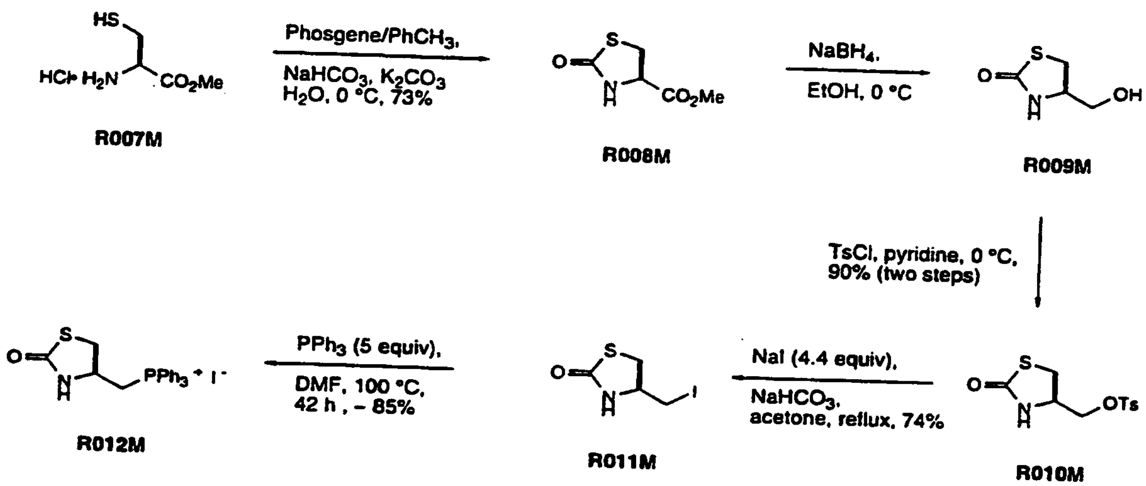

CBr4, PPh3,
CH2Cl2
KSAc,
DMF
1. K2CO3, MeOH
2. nBu3P, THF, H2O
R008T
K2CO3, MeOH
LiOH, H2O,
dioxane
HCl•H2N-Met-CO2Me,
EDC, HOBT, NMM,
DMF
MeO2CSCl,
HOAc, DMF, H2O
1. nBu3P, THF, H2O
2. TFA, Et3SiH
R019D
R001T
R002T
R003T
R004T
R005T
R006T
R007T
PT011

Scheme VIII

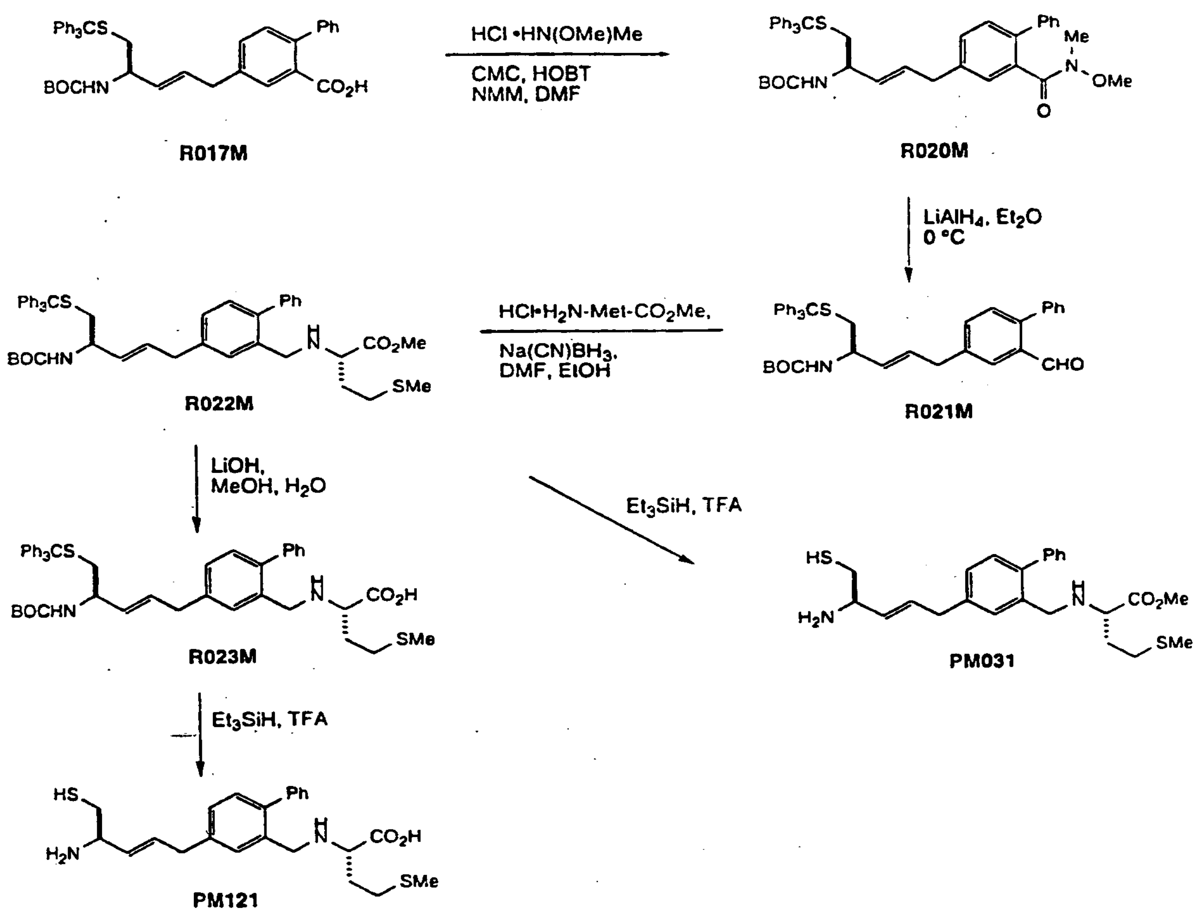


OH
OHC
CO_2H
R001M
MeOH, H_2SO_4,
reflux
OH
OHC
CO_2Me
R002M
Tf_2O, pyridine
0 °C
OTf
OHC
CO_2Me
R003M
$PhB(OH)_2$,K_2CO_3,
Pd catalyst, toluene, 100 °C
Ph
OHC
CO_2Me
R004M
$Ph_3PCH_2OMe^+ Cl^-$
KOtBu/THF,
THF, ca. 0 °C -> rt
Ph
MeO
CO_2Me
R005M
TsOH,
dioxane, H_2O
85 °C
Ph
OHC
CO_2Me
R006M
R012M, LiHMDS, nBuLi,
THF, –45°C -> room temp
O
S
N
H
Ph
CO_2Me
R013M *cis*
R013M *trans*
BOC_2O,
cat. DMAP
THF
O
S
N
BOC
Ph
CO_2Me
R014M
1. Cs_2CO_3, $CsHCO_3$, MeOH
2. nBu_3P, H_2O, THF
HS
BOCHN
Ph
CO_2Me
R015M
Ph_3COH, BF_3•OEt_2,
Et_2O, 0 °C
Ph_3CS
BOCHN
Ph
CO_2Me
R016M
LiOH, H_2O, MeOH, reflux
Ph_3CS
BOCHN
Ph
CO_2H
R017M
HCl • H_2N-Met-CO_2PNB
CMC, HOBT
NMM, DMF
Ph_3CS
BOCHN
Ph
H
N
CO_2PNB
O
SMe
R018M
1. Na_2S, H_2O, THF
2. RP HPLC
Ph_3CS
BOCHN
Ph
H
N
CO_2H
O
SMe
R019M
1. TFA, Et_3SiH
2. RP HPLC
HS
H_2N
Ph
H
N
CO_2H
O
SMe
PM061

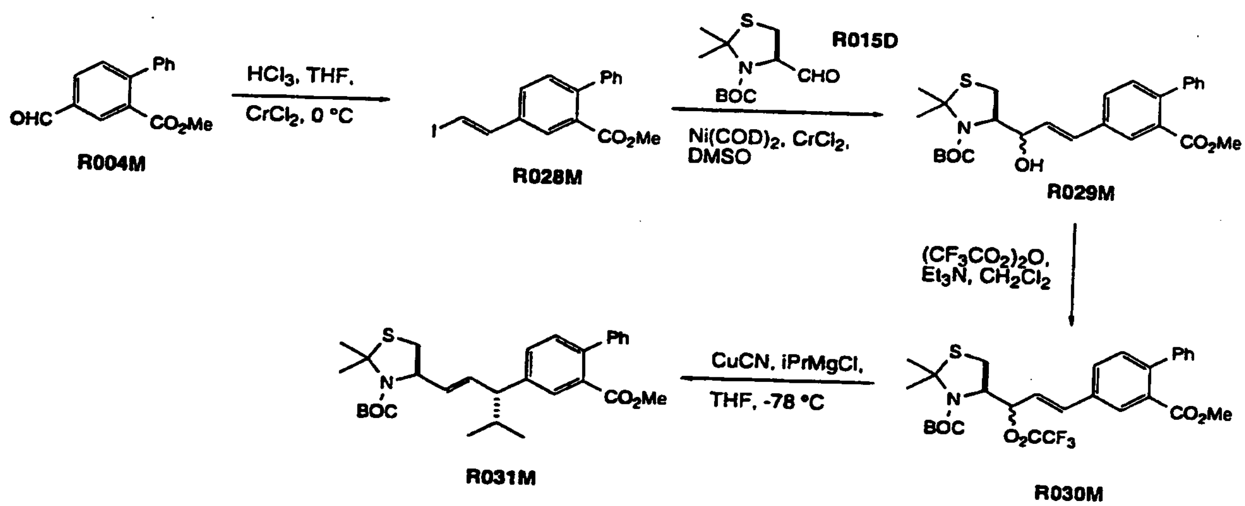
Scheme IX


HS
HCl• H2N CO2Me
R007M
Phosgene/PhCH3,
NaHCO3, K2CO3
H2O, 0 °C, 73%
S
O
N
H
CO2Me
R008M
NaBH4,
EtOH, 0 °C
OH
R009M
TsCl, pyridine, 0 °C,
90% (two steps)
OTs
R010M
NaI (4.4 equiv),
NaHCO3,
acetone, reflux, 74%
I
R011M
PPh3 (5 equiv),
DMF, 100 °C,
42 h, ~ 85%
PPh3+ I−
R012M

Scheme X


Ph3CS
BOCHN
Ph
CO2H
R017M
HCl •HN(OMe)Me
CMC, HOBT
NMM, DMF
Ph
Me
N
OMe
O
R020M
LiAlH4, Et2O
0 °C
CHO
R021M
HCl•H2N-Met-CO2Me,
Na(CN)BH3,
DMF, EtOH
CO2Me
SMe
R022M
LiOH,
MeOH, H2O
R023M
Et3SiH, TFA
HS
H2N
PM031
PM121

Scheme XI


Ph
OHC
CO2Me
R004M
HCl3, THF,
CrCl2, 0 °C
I
Ph
CO2Me
R028M
S
N
BOC
CHO
R015D
Ni(COD)2, CrCl2,
DMSO
S
N
BOC
OH
Ph
CO2Me
R029M
(CF3CO2)2O,
Et3N, CH2Cl2
S
N
BOC
O2CCF3
Ph
CO2Me
R030M
CuCN, iPrMgCl,
THF, -78 °C
S
N
BOC
Ph
CO2Me
R031M

E. *In vitro* and *in vivo* data demonstrating utility

Ras proteins mediate the transformation of normal cells to cancer cells in many human cancers. Before becoming membrane associated and fully functional, ras proteins require post-translational processing. Compounds which inhibit prenylation will, therefore, inhibit the growth of ras-related cancers.

Compounds of the invention were screened in four art-accepted *in vitro* assays. First, each of over 60 tested inhibitor compounds was shown to inhibit FTase-mediated prenylation (Table 1). Second, each of over 60 tested compounds was shown to inhibit GGTase-mediated prenylation (Table 1). Third, each of over 60 tested compounds was shown to inhibit ras protein processing in whole cells (Table 2). Clearly, the compounds of the invention inhibit the prenylating activity of FTase, GGTase, or in most cases, both enzymes, with different potencies.

Furthermore, the compounds of the invention inhibit the anchorage-independent growth of ras-related tumor cell lines. For example, PD331 was shown to inhibit the growth of five tumor cell lines (Table 3). HT1080 is a neurofibrosarcoma with a N-ras mutation. MIApaca-2 is a pancreatic carcinoma and Sw620 is a colonic carcinoma; each of these has a K-ras mutation. T24 is a bladder carcinoma with a H-ras mutation; and zH1 is a H-ras-transformed NIH/3T3 mouse fibroblast. Additional compounds have been tested and have yielded positive results in these organ-specific or ras-protein specific anchorage-independent tumor cell models.

More importantly, an *in vivo* experiment demonstrated that compound PD331 effectively inhibited the growth of ras-associated tumors in mice (Table 4). The results of a second *in vivo* experiment demonstrated that another compound

(PM061) effectively inhibited the growth of ras-associated tumors in mice (Table 5).

Thus, the ability of the compounds of the invention to inhibit protein processing has been demonstrated in three separate *in vitro* assays. The ability of the compounds of the invention to inhibit ras-related cancer growth has been demonstrated in an *in vitro* assay and two separate *in vivo* experiments. The compounds of the invention are effective inhibitors of ras-related cancers.

A. Inhibition of FTase and GGTase Prenylation

The ability of the disclosed inhibitor compounds to inhibit FTase was measured according to a published prenylation assay (Moores et al., *J. Biol. Chem.* 266:14603 (1991). Partially purified FTase with 3 μM recombinant H-ras and 440 nM [^{3}H]FPP (FTase) were used. The inhibitors were diluted in assay buffer, and each assay mixture was incubated 15 min. at 37 °C. Where inhibition of GGTase was measured, partially purified GTTase with 5 μM recombinant H-ras (61L, CAIL) and 1 μM [^{3}H] geranylgeranyl diphosphate were used.

The IC_{50} (concentration of compound needed to cause 50% inhibition) values are presented in Table 1. Nanomolar concentrations of the indicated compounds were sufficient to inhibit farnesylation of ras proteins *in vitro*. For screening candidate compounds useful for the treatment of ras-associated tumors, the FTase assay is preferred. One embodiment of the invention selectively inhibits FTase. Substitutions which confer GGTase specificity as taught herein also produced potent inhibitors of GGTase.

TABLE 1

Compound	IC_{50} μM FTase	GGTase
PA011	0.140	11.0
PA021	0.028	7.1
PA031	0.0036	0.215
PA041	0.0025	0.056
PA051	0.020	0.076
PA061	0.0021	0.048
PA071	0.022	0.5
PA081	0.102	2.66
PA091	0.170	2.38
PA101	0.170	1.30
PA111	0.013	0.27
PA121	0.015	0.38
PA131	0.028	1.8
PA141	0.095	0.880
PD012	0.038	0.62
PD022	0.0052	3.065
PD032	0.45	2.86
PD042	0.005	1.62
PD052	2.81	8.05
PD062	0.2	1.76
PD072	0.042	0.68
PD082	1.57	>10
PD092	0.052	3.2
PD102	0.394	>10
PD112	2.22	8.05
PD122	0.003	0.010
PD421	0.57	3.4
PD431	0.006	1.08
PD441	0.026	0.17
PD451	0.146	1.11
PE011	0.043	1.030
PE021	0.009	0.092
PE031	0.020	0.14
PE041	0.027	0.160
PE051	0.29	2.30
PE061	0.060	6.30
PM011	1.13	1.6
PM012	0.002	0.520
PM021	0.017	0.075
PM022	0.018	0.130
PM031	0.115	1.40
PM032	0.093	6.59
PM041	0.18	1.4
PM042	3.1	0.32
PM051	0.00085	1.55
PM052	0.0003	0.19
PM061	0.007 (12)	0.144 (3)
PM062	0.009	0.42
PM071	0.71	0.95
PM072	0.16	3.96
PM081	0.17	1.68
PM082	0.03	0.148

PD132	0.245	4.77
PD142	0.042	2.12
PD152	0.023 (12)	0.044(5)
PD162	0.26	4.57
PD172	0.007	0.75
PD182	<0.001	0.0633 (4)
PD192	0.296	2.99
PD202	0.017	1.12(3)
PD212	0.003	0.0045
PD222	0.71	3.04
PD301	0.002	0.0037
PD311	0.069(6)	0.57
PD321	0.025	0.014
PD331	0.011 (22)	0.013 (11)
PD341	0.0002	0.0076
PD351	0.32	2.49
PD361	0.0001	0.016
PD371	0.038	0.112
PD381	0.080	0.0710
PD391	0.0290	0.0550
PD401	0.028	1.40
PD411	0.56	8.4

PM091	0.002	>1.0
PM092	0.215	3.50
PM101	0.024 (8)	0.793 (3)
PM102	0.29	4.85
PM111	0.024	0.246
PM112	0.0012	1.66
PM121	0.022	1.72
PM122	0.003	2.2
PM131	0.605	0.0024
PM132	0.119	1.63
PM141	0.0001	0.016
PM142	0.008	0.072
PM151	0.605	3.87
PM152	0.038	0.270
PM161	0.0009	2.14
PM162	0.0018	0.12
PM172	0.056	0.123
PM182	0.017	0.52
PM192	0.280	3.79
PM202	0.016(2)	7.42(2)
PM212	0.056	1.84
PT011	0.043	0.638

B. Inhibition of Prenylation in Whole Cells

The ability of compounds of the invention to inhibit H-ras farnesylation and rap1 geranylgeranylation in whole cells was determined. H-ras (61L) transformed NIH3T3 fibroblasts were generously provided by C. Der, Univ. N. Carolina. These fibroblasts were treated for 24 h with 50 μM lovastatin (control) or the indicated concentrations of inhibitor. The cells were lysed in 1% NP-40, 5 mM Tris-HCl (pH 8.0), 5 mM EDTA, 0.1 mM *N*-tosyl-L-phenylalanine chloromethyl ketone, 0.1 mM *N*-tosyl-L-lysine chloromethyl ketone, and 1 mM phenylmethylsulfonyl fluoride. The lysate was centrifuged (15000 x *g*, 5 min.) and the supernatant was used as a cell extract. Total protein was separated by SDS-PAGE in 15% acrylamide gel. After transfer to IMMOBILON P™ membrane (Millipore), the blots were probed with LA069 mouse monoclonal antibody to H-ras (Quality Biotech), or rabbit polyclonal antibody to rap1/Krev (Santa Cruz Biotechnology). All Western blots were developed using ECL chemiluminescent reagents (Amersham).

The IC_{50} values for H-ras are presented in Table 2. Sub-micromolar concentrations of the indicated compounds are sufficient to inhibit farnesylation of ras proteins in whole cells. In contrast, inhibition of geranylgeranylation of rap1 required compound concentrations in excess of 100 μM (data not shown). Thus, many compounds of the invention inhibit farnesylation more specifically than geranylgeranylation.

TABLE 2

Analog	H-ras $IC_{50}\mu M$
PA011	0.1
PA021	0.08
PA031	1.0
PA041	3.5
PA051	1.9
PA061	0.58
PA071	3.1
PA081	0.025
PA091	0.1
PA101	0.24
PA111	0.13
PA121	0.58
PA131	0.039
PA141	0.017
PD012	72
PD022	0.4
PD032	1.95
PD042	1.95
PD062	21
PD072	7.4
PD092	0.78
PD102	75
PD112	193
PD122	0.4
PD132	2.6
PD142	7.3

Analog	H-ras $IC_{50}\mu M$
PD441	4.2
PD451	0.4
PE011	0.01
PE021	0.28
PE031	0.33
PE041	0.19
PE051	0.11
PE061	1.1
PM011	>100
PM012	2.7
PM021	2.1
PM022	13.1
PM031	25
PM032	19.5
PM041	2.3
PM042	>500
PM051	23.5
PM052	2.6
PM061	4.8
PM062	0.36
PM071	>100
PM072	2.4
PM081	23.4
PM082	21
PM091	474
PM092	2.7

PD152	0.32
PD162	326
PD172	13.1
PD182	2.8
PD192	0.18
PD202	1.95
PD212	0.11
PD222	>50
PD301	4.5
PD311	0.1-1
PD321	0.1-1
PD331	0.4
PD341	0.29
PD351	3.3
PD361	3.5
PD371	0.09
PD381	~1
PD391	16.4
PD401	0.1-1
PD411	0.22
PD421	1.90

PM101	14.6
PM102	26
PM111	>100
PM112	4.0
PM121	23.4
PM122	23.4
PM131	>250
PM132	1.6
PM141	9.7
PM142	1.1
PM151	2.9
PM152	40.3
PM161	18.9
PM162	13.1
PM172	>100
PM182	2.7
PM192	0.23
PM202	1.2
PM212	0.045
PT011	0.023

C. Inhibition of Anchorage-Independent Tumor Cell Growth

Five tumor cell lines were seeded at 600 cells/well (12-well plates) in 0.6 mL of 0.3% Noble agar in culture medium over a bottom agar layer (0.5% Noble agar in culture medium). The culture medium was Dulbecco's modified Eagle's medium (Nissui Pharmaceutical Co., Ltd., Tokyo, Japan), supplemented with 10% heat-inactivated calf serum (GIBCO, Grand Island, NY). A 10 mM stock solution of inhibitor compound **PD331** in DMSO was diluted with culture medium to 3x the final concentration and 0.6 mL of the diluted inhibitor solution was overlayed on each well. Controls contained the same amount of DMSO as inhibitor samples. Plates were incubated at 37 °C in 5% CO_2 for 14 days. Colonies were counted by replacement of the overlaying medium with 0.6 mL of 2 mg/mL MTT in PBS, incubation for 30 min, and quantitation of scanned photographs. IC_{50} concentrations for each cell line are shown below in Table 3.

TABLE 3

Cell Line	IC_{50} (μM)
HT1080	1.8
MIApaca-2	19
Sw620	22
T24	0.3
zH1	0.6

D. Inhibition of human tumor xenograft in mice

H-ras (61L) transformed NIH3T3 fibroblasts were grown in Dulbecco's modified Eagle's medium supplemented with 10% heat-inactivated calf serum. 100 U/mL penicillin, 100 μg/mL streptomycin, and 0.75 mg/mL G418 (GIBCO) and incubated at 37 °C in 5% CO_2. Cells were harvested from exponential-phase maintenance cultures (T-225 cm^2 culture flasks, Corning Inc., Corning, NY) with trypsin-EDTA (GIBCO), centrifuged at 160 x *g* for 5 min, washed once with 10 mL cold Hank's balanced salt solution (HBSS, GIBCO), and resuspended at a concentration of 1×10^6 cells/mL.

Five week old female athymic nude mice were obtained from SLC (3371-8, Kotoummachi, Hamamatsu-shi, Shizuoka 431-11, Japan) and maintained under pathogen-free conditions. The mice were subcutaneously injected in the lateral flank with 1×10^5 H-ras transformed cells/mouse.

Inhibitor compound PD331 was suspended in saline containing 2% Tween-80 in a total injection volume of 0.2 mL. Two dosage concentrations were prepared, 0.3 mg/mouse or 1.0 mg/mouse. Compound PD331 was subcutaneously injected daily at the site of tumor cell implantation for 5 consecutive days, starting approximately 8 h after the implantation (day 0). The control group was injected with vehicle only. Body weight and tumor dimensions were measured at days 7, 10, and 14. Tumor volume was estimated by the following calculation: tumor volume = (0.5)(length x width x width). At day 14, each mouse was euthanized with $CO_2(g)$, and each tumor was excised and weighed. The statistical significance was estimated by the Student's T-test. Final tumor volumes are presented in Table 4.

TABLE 4

Sample	Dosage	Tumor volume (μl)	T/C(%) Volume
Control	vehicle	1634.40±527.93	100
PD331	0.3 mg/mouse	871.28±526.90	53.3
PD331	1.0 mg/mouse	269.55±292.95	16.5

Compound **PD331** has a significant effect on H-ras tumor growth in mice. At every concentration, both the weight and the volume of the tumors from the treated group were less than the weight and volume of tumors from the control group. These data clearly demonstrate that the compounds of the invention inhibit the formation and growth of *in vivo* tumors caused by the ras oncogene.

E. Inhibition of human tumor xenograft in mice

The same *in vivo* experiment as Example D above was performed, using compound **PM061**. Instead of 0.3 mg/mouse and 1.0 mg/mouse, three injection concentrations were prepared (0.5 mg/mouse, 1.0 mg/mouse, and 2.0 mg/mouse). Body weight and tumor size were measured at days 7, 10, and 15. Tumors were excised at day 15. Final tumor volumes are presented in Table 5.

Compound **PM061** had a significant effect on H-ras tumor growth in mice. An injection of 2.0 mg of compound **PM061** decreased the tumor volume to 53.2% of the tumor volume in the control mouse. These data clearly demonstrate that the compounds of the invention inhibit the formation and growth of *in vivo* tumors caused by the ras oncogene.

TABLE 5

Sample	Dosage	Tumor Volume (μl)	T/C(%) Volume
Control	vehicle	2613.6±462.8	100
PM061	0.5 mg/mouse	2360.4±645.0	90.3
PM061	1.0 mg/mouse	2660.3±756.4	101.8
PM061	2.0 mg/mouse	1400.6±703.2	53.6

F. Use

The disclosed compounds are used to treat ras-associated tumors in mammals, and particularly humans. The disclosed compounds are also used to treat tumors or other conditions mediated by (i) a farnesylated protein, such as ras, lamin B, or γ-transducin, (ii) a geranylgeranylated protein, such as Rap, Rab, or Rho, or (iii) a combination thereof.

The claimed pharmaceutically acceptable salts may be formed, for example, with 1, 2, 3, or more equivalents of hydrogen chloride, hydrogen bromide, trifluoroacetic acid, and others known to those in the art of drug formulation. Compounds of the invention can be formulated into pharmaceutical compositions by admixture with pharmaceutically acceptable non-toxic excipients and carriers. A pharmaceutical composition of the invention may contain more than one compound of the invention, and/or may also contain other therapeutic compounds not encompassed by the invention, such as anti-cancer agents. Another aspect of the invention is a packaged drug, containing a pharmaceutical composition formulated into individual dosages and printed instructions for self-administration.

Compounds of the invention may be prepared for use in parenteral administration, particularly in the form of

solutions or liquid suspensions; for oral administrations, particularly in the form of tablets or capsules; or intranasally, particularly in the form of powders, gels, oily solutions, nasal drops, aerosols, or mists. A compound of the invention may be administered in unit dosage form, and may be prepared by any of the methods well known in the pharmaceutical art, for example, as described in *Remington's Pharmaceutical Sciences* (Mack Pub. Co., Easton, PA, 1980).

Formulations for parenteral administration may contain as common excipients sterile water or sterile saline, polyalkylene glycols such as polyethylene glycol, oils of vegetable origin, hydrogenated naphthalenes, and the like. Controlled release of a compound of the invention may be obtained, in part, by use of biocompatible, biodegradable polymers of lactide, and copolymers of lactide/glycolide or polyoxyethylene/polyoxypropylene. Additional parental delivery systems include ethylene-vinyl acetate copolymer particles, osmotic pumps, implantable infusion systems, and liposomes.

Formulations for inhalation administration contain lactose, polyoxyethylene-9-lauryl ether, glycocholate, or deoxycholate. Formulations for buccal administration may include glycocholate; formulations for vaginal administration may include citric acid.

The concentration of a disclosed compound in a pharmaceutically acceptable mixture will vary depending on several factors, including the dosage of the compound to be administered, the pharmacokinetic characteristics of the compound(s) employed, and the route of administration. In general, the compounds of this invention may be provided in an aqueous physiological buffer solution containing about 0.1 to 10% w/v of compound for parenteral administration. Typical dose ranges are from about 0.1 to about 250 mg/kg of

body weight per day, given in 2-4 divided doses. Each divided dose may contain the same or different compounds of the invention. The dosage will be an effective amount depending on several factors including the type and extent of cancer metastasis, the overall health of a patient, and the formulation and route of administration of the selected compound(s).

Without further elaboration, it is believed that one skilled in the art can, based on the description herein, utilize the present invention to its fullest extent. The following specific examples are, therefore, to be construed merely as illustrative, and not limitative of the disclosure in any way whatsoever. Publications mentioned herein are hereby incorporated by reference.

Example 1

Synthesis of Alcohols R003D

A 1.0 M solution of DIBAL in hexanes (87 mL, 87 mmol) was added dropwise to a solution of amide R001D (17.7 g, 34.9 mmol, prepared from condensation of *N*-BOC, *S*-trityl cysteine and *N,O*-dimethyl hydroxylamine hydrochloride using hydroxybenzotriazole hydrate [HOBT], dicyclohexylcarbodiimide [DCC], and *N*-methylmorpholine [NMM] in dimethylformamide [DMF]) in anhydrous toluene (230 mL). The reaction mixture was stirred at -78°C for 30 min, quenched with methanol (80 mL), and then allowed to warm to room temp. Saturated aqueous sodium potassium tartrate (100 mL) was added and the resulting two-phase mixture stirred rapidly at room temp for 45 min. CELITE® was added, the mixture was filtered through a pad of CELITE®, and the filter pad then was washed well with ethyl acetate. The aqueous phase was extracted with ethyl acetate. The combined organic phases were dried with brine, dried over $MgSO_4$, filtered, concentrated, and azeotroped two times with anhydrous toluene (15 mL) to afford the protected cysteine aldehyde.

To a solution of E-4-tertbutyldimethylsilyloxy-tri-*n*-butylstannylpropene (65.0 g, 14.09 mmol) in anhydrous tetrahydrofuran (THF) (230ml) at -78°C was added a 2.5 M solution of *n*-butyllithium in hexanes (58.6 mL, 146.5 mmol) dropwise. After the addition was complete, the reaction mixture was stirred an additional 1 h at -78°C to complete transmetalation to lithiated olefin R002D. A solution of the protected cysteine aldehyde, described above, in anhydrous THF (50 mL, precooled to -78°C) was added to olefin R002D by cannula. The orange-red reaction mixture was allowed to stir for an additional 15 min. after completion of the addition. The solution then was quenched

by addition of saturated aqueous NH_4Cl (60 mL), and allowed to warm to room temp. After extraction with ethyl acetate, the organic phases were dried with brine, dried over $MgSO_4$, filtered, and concentrated to a yellow liquid (~90 g). The crude product was partially purified by chromatography on silica, eluting with a (10-30%) ethyl acetate-hexanes gradient to afford the alcohols **R003D** (9.53 g, 44%). The following characteristic values may be obtained by nuclear magnetic resonance spectroscopy:

^1H NMR ($CDCl_3$) δ: 7.1 - 7.5 m, 5.72 m, 5.53 dd (one isomer, J = 6.1, 14.3 Hz), 5.45 dd (J = 6.1, 14.3 Hz), 4.11 dd (J = 6.4, 7.9 Hz), 1.43 s (one isomer), 1.40 s (one isomer), 0.89 s, 0.04 s.

Example 2

Synthesis of Oxazolidinones R004D

Alcohols **R003D** (11.7 g, 18.9 mmol) were added to a suspension of hexane washed NaH (1.03 g, 42.8 mmol) in anhydrous THF (100 mL) by cannula, and the resulting mixture was stirred overnight. The reaction was quenched with saturated aqueous NH_4Cl and diluted with both water and ethyl acetate. After separation of the phases, the organic phase was washed with phosphate buffer (pH 7.2). The combined aqueous phases were extracted with ethyl acetate. The combined organic phases were dried once with brine, dried over Na_2SO_4, filtered, and then concentrated to a dark foam (10.51 g). The dark foam was purified by flash chromatography on silica gel (FC), eluting with 25% ethyl acetate-hexanes. Oxazolidinones **R004D** (6.59 g, 64%) were obtained as a yellow foam. The following characteristic values may be obtained by nuclear magnetic resonance spectroscopy:

^{1}H NMR ($CDCl_3$) δ: 7.1-7.5 m, 5.85 dt (one isomer, J = 4.7, 14.8 Hz), 5.77 (one isomer, J = 4.7, 14.8 Hz), 5.55 m, 4.84 t (one isomer, J = 7.3 Hz), 4.43 t (one isomer, J = 6.2 Hz), 4.16 m, 3.08 q (one isomer, J = 7.5 Hz), 2.96 q (one isomer, J = 4.7 Hz), 0.91 s (one isomer), 0.89 s (one isomer), 0.07 s, 0.04 s.

Example 3

Synthesis of Oxazolidinone R005D

Di-t-butyldicarbonate (3.95 g, 18.1 mmol) was added to a solution of oxazolidinone R004D (6.59 g, 12.1 mmol) and DMAP (300.4 mg, 1.46 mmol) in anhydrous THF (100 mL) that was maintained at 0°C. After 15 min, the reaction mixture was allowed to warm to room temp and stirred for an additional 45 min. After dilution with ethyl acetate and water, the phases were separated, and the aqueous phase was extracted with ethyl acetate. The combined organic phases were dried with brine, dried over Na_2SO_4, filtered, and concentrated to a yellow oil. The mixture of oxazolidinones was purified and separated by FC, eluting with 15% ethyl acetate-hexanes to afford first the α alkoxy isomer (2.30 g, 36%) followed by the desired oxazolidinone R005D (3.71 g, 47%). The following characteristic values may be obtained by nuclear magnetic resonance spectroscopy:

^{1}H NMR ($CDCl_3$) δ: 7.1-7.4 m, 5.91 dt (J = 15.4, 3.9 Hz), 5.81 ddt (J = 6.8, 15.5, 3.5 Hz), 4.29 m, 4.19 m, 2.53 dd (J = 7.5, 12.1 Hz), 2.22 dd (J = 3.7, 12.2), 1.48 s, 0.88 s, 0.44 s.

Example 4

Synthesis of Olefin R006D

To a slurry of CuCN (2.06, 23.0 mmol) in anhydrous THF (75 mL) at -40°C was added a 2 M solution of *i*-PrMgCl in THF (11.50 mL, 23.0 mmol). The reaction mixture was stirred at -40°C for 10 min and then at 0°C for 20 min. The resulting black mixture was cooled to -78°C and $BF_3 \cdot OEt_2$ (2.80 mL, 22.8 mmol), added dropwise. After stirring for 5 min, a solution of oxazolidinone **R005D** (3.71 g, 5.74 mmol) in anhydrous THF (25 mL) was added by cannula, and the resulting mixture was stirred for 1 h at -78°C. A mixture of a saturated aqueous solution of NH_4Cl (70 mL) and NH_4OH (35 mL) was added by cannula, and the reaction mixture was allowed to warm to room temp. Ethyl acetate was added, and the biphasic mixture was stirred vigorously for 15 min then extracted with ethyl acetate. The organic phase was washed with water, phosphate buffer (pH 7.2), and the combined aqueous phases were back-extracted with ethyl acetate. The combined organic phases were dried with brine, dried over Na_2O_4, filtered, and concentrated to a yellow oil. The crude product was purified by FC, eluting with 10% ethyl acetate-hexanes to afford the desired olefin **R006D** as yellow foam (2.64 g, 71%). The following characteristic values may be obtained by nuclear magnetic resonance spectroscopy:

^{1}H NMR ($CDCl_3$) δ: 7.42 d (J = 8.0 Hz), 7.29 t (J = 7.3 Hz), 7.22 t (J = 7.2 Hz), 5.39 dd (J = 8.7, 15.2 Hz), 5.27 dd (J = 5.9, 15.4 Hz), 4.57 bs, 4.18 bs, 3.54 ab q, 2.38 bm, 2.33 bm, 1.92 m. 1.79 octet (J ~ 7 Hz), 1.43 s, 0.87 s, 0.80 d (J = 6.8 Hz), 0.01 s.

Example 5

Synthesis of Alcohol R007D

A solution of silyl ether R006D (2.64 g, 4.09 mmol) and tetrabutylammonium fluoride (TBAF) (2.69 g, 10.28 mmol) in anhydrous THF (40 mL) was stirred for 5 h at room temp. The reaction mixture was diluted with ethyl acetate and washed with pH 7.2 phosphate buffer. The organic layer was dried with brine, dried over Na_2SO_4, filtered, and concentrated to afford a dark oil. The crude product was purified by FC, eluting with 25% ethyl acetate-hexanes to afford the desired alcohol R007D as a yellow oil (2.24 g, >100%). The following characteristic values may be obtained by nuclear magnetic resonance spectroscopy:

^1H NMR ($CDCl_3$) δ: 7.41 d (J = 7.0 Hz), 7.28 t (J = 7.5 Hz), 7.21 t (J = 6.5 Hz), 5.33 dd (J = 5.5, 15.2 Hz), 5.27 dd (J = 8.2, 15.5 Hz), 4.60 bs, 4.10 bs, 3.63 dd (J = 4.6, 10.8 Hz), 3.34 dd (J = 9.10, 10.5 Hz), 2.43 bm, 2.27 bm, 1.93 m. 1.60 octet (J ~ 7 Hz), 1.41 s, 0.87 d (J = 6.8 Hz), 0.85 d (J = 6.8 Hz).

Example 6

Synthesis of Aldehyde R008D

A solution of alcohol R007D (2.24 g, 4.09 mmol) and PCC (1.754 g, 8.14 mmol) was stirred in CH_2Cl_2 (40 mL) at room temp for 4 h. Solvent was removed under vacuum, and the residual material was slurried in CH_2Cl_2-methanol. This slurry was pipetted into a rapidly stirring suspension of CELITE® in ether, and the mixture was filtered. The filtrate was concentrated, and the residue was precipitated as before, but without the use of methanol. After filtration and concentration, a yellow-green oil was obtained which was promptly purified by FC, eluting with 15% ethyl acetate-hexanes. The aldehyde R008D (2.39 g, >100%)

was obtained as a pale yellow oil. The following characteristic values may be obtained by nuclear magnetic resonance spectroscopy:

^{1}H NMR ($CDCl_3$) δ: 7.41 d (J = 7.0 Hz), 7.28 t (J = 7.5 Hz), 7.21 t (J = 6.5 Hz), 5.33 dd (J = 5.5, 15.2 Hz), 5.27 dd (J = 8.2, 15.5 Hz), 4.60 bs, 4.10 bs, 3.63 dd (J = 4.6, 10.8 Hz), 3.34 dd (J = 9.10, 10.5 Hz), 2.43 bm, 2.27 bm, 1.93 m, 1.60 octet (J ~ 7 Hz), 1.41 s, 0.87 d (J = 6.8 Hz), 0.85 d (J = 6.8Hz).

Example 7

Synthesis of Alcohols R009D

Aldehyde R008D (2.39 g, <4.09 mmol) and methyl *E*-3-iodo-acrylate were placed in a flask, flushed with argon, capped, and transferred to a dry box. Anhydrous freshly distilled THF (20 mL) was added, followed by slow, portionwise addition of 0.5% $NiCl_2$:$CrCl_2$ (1.52 g, 12.4 mmol). After 4 h, the dark mixture was removed from the dry box and diluted with saturated aqueous NH_4Cl and $CHCl_3$. The resulting slurry was stirred rapidly overnight. After separation of the phases, the organic phase was washed once with water and once with phosphate buffer (pH 7.2) which resulted in an emulsion. After removal of the emulsion by filtration through CELITE® and clean separation of the resulting two phases, the organic phase was dried once with brine, dried over Na_2SO_4, filtered, and concentrated to a yellow-green semisolid. Repeated purification by FC, eluting with 15% ethyl acetate-hexanes afforded the desired alcohols R009D as colorless oils (524 mg, 21% overall from R006D). The following characteristic values may be obtained by nuclear magnetic resonance spectroscopy:

^1H NMR ($CDCl_3$) δ isomer I: 7.40 d (J = 7.5 Hz), 7.29 t (J = 7.5 Hz), 7.21 t (J = 7.3 Hz), 6.98 dd (J = 4.4, 15.6 Hz), 6.02 dd (J = 1.7, 15.6 Hz), 5.32 dd (J = 6.1, 15.2 Hz), 5.16 dd (J = 10.1, 15.3 Hz), 4.58 bs, 4.34 bs, 4.02 bs, 3.70 s, 2.46 dd (J = 5.5, 11.5 Hz), 2.34 bd (J = 9.7 Hz), 2.20 bs, 1.98 dt (J = 4.8, 15.2 Hz), 1.68 bm, 1.40 s, 0.96 d (J = 6.6 Hz), 0.84 d (J = 6.6 Hz).

Example 8

Synthesis of Mesylates R010D

A solution of Et_3N (246 μL, 1.77 mmol) was added to a solution of alcohol **R009D** (229.6 mg, 0.37 mmol) in anhydrous CH_2Cl_2 (7.5 mL) at 0°C under N_2. A solution of methanesulfonyl chloride (129 μL, 1.68 mmol) then was added to the mixture, and the reaction was allowed to warm to room temp. After dilution with ethyl acetate (25 mL) and saturated aqueous NH_4Cl, the organic phase was separated, dried with brine, dried over $MgSO_4$, filtered, and concentrated to a yellow oil. This oil was purified by FC, eluting with a 15-25% ethyl acetate-hexanes gradient. Mesylates **R010D** (252 mg, 98%) were obtained as a colorless oil. The following characteristic values may be obtained by nuclear magnetic resonance spectroscopy:

^1H NMR ($CDCl_3$) δ: 7.39 d (J = 7.2 Hz), 7.28 t (J = 7.4 Hz), 7.21 t (J = 6.7 Hz), 6.80 dd (J = 6.4, 15.7 Hz), 6.06 bd (J = 15.6 Hz), 5.31 dd (J = 6.1, 15.2 Hz), 5.21 b, 4.58 bs, 4.11 q (J = 7.0 Hz), 3.68 s, 2.90 s, 2.43 bs, 2.22 bm, 1.82 m, 1.40 s, 0.92 d (J = 6.5 Hz), 0.85 d (J = 6.5 Hz).

Example 9

Synthesis of Diene R011D

A 2 M solution of benzyl magnesium chloride (335 μL, 2.72 mmol) in THF was added dropwise to a suspension of CuCN (256.5 mg, 2.86 mmol) in anhydrous THF (7.5 mL) maintained at -40°C under Argon. The reaction mixture was stirred for 20 min at -40°C, and then warmed to 0°C for 20 min. The resulting dark, opaque mixture was cooled to -78°C and $BF_3 \cdot OEt_2$ (335 μL, 2.72 mmol) was added dropwise. After 5 min, a solution of mesylates **R010D** (186.1 mg, 0.27 mmol) in anhydrous THF (2 mL + 2 mL rinse) was added. After 15 min, the reaction was quenched with saturated aqueous NH_4Cl and NH_4OH (1:1 v/v) and allowed to warm to room temp. It then was diluted with ethyl acetate, stirred vigorously for 15 min, diluted further with both ethyl acetate and water, and the phases were separated in a separatory funnel. The organic phase was washed with pH 7.2 phosphate buffer. The aqueous phase was back extracted with ethyl acetate, and the combined organic phases were dried with brine, dried over $MgSO_4$, filtered, and concentrated to a yellow oil. After purification by FC, eluting with 10% ethyl acetate-hexanes, a mixture of the benzyl isomers of diene **R011D** (157.7 mg, 85%) was obtained. The isomers were separated after further purification by HPLC on silica, eluting with 5% ethyl acetate-hexanes to afford pure major β isomer **R011D** (~80 mg, 43%) as well the minor α isomer (43 mg, 23%). The following characteristic values may be obtained by nuclear magnetic resonance spectroscopy:

^1H NMR ($CDCl_3$) δ major isomer: 7.09 - 7.40 m, 5.46 t (J = 10.4 Hz), 5.35 t (J = 10.5 Hz), 5.27 ddd (J = 1.2, 7.5, 15.4 Hz), 4.91 dd (J = 5.0, 15.2 Hz), 4.47 bs, 4.09 bs, 3.60 s, 3.55 q (J = 8.3 Hz), 3.00 dd (J = 7.5, 13.5 Hz), 2.75 dd

(J = 7.4, 13.5 Hz), 2.64 q (J = 8.1 Hz), 2.29 bm, 2.25 bm, 1.52 o (J = 7.5 Hz), 1.42 s, 0.81 d (J = 6.7 Hz), 0.78 d (J = 6.7 Hz).

^{1}H NMR ($CDCl_3$) δ minor isomer: 7.04 - 7.43 m, 5.34 m, 4.97 ddd (J = 0.6, 6.3, 15.3 Hz), 4.51 bs, 4.12 bs, 3.61 s, 3.28 q (J = 7.8 Hz), 3.07 dd (J = 7.2, 13.6 Hz), 2.76 dd (J = 8.0, 13.6 Hz), 2.39 q (J = 6.9 Hz), 2.34 bm, 2.29 bm, 1.54 o (J = 6.6 Hz), 1.44 s, 0.75 d (J = 6.7 Hz).

Example 10

Synthesis of Acid **R012D**

A solution of LiOH (11.5 mg, 480 μmol) in water (5.0 mL) was added to a solution of methyl ester **R011D** (110 mg, 160 μmol) in dioxane (5.0 mL), and the reaction was stirred for 12 h at room temp under N_2. Additional LiOH (11.5 mg, 480 μmol) then was added, and the reaction was stirred for an additional 3 h. The reaction was acidified to pH 2 with 1 M $KHSO_4$, and then extracted with ethyl acetate. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and then concentrated to acid **R012D** (85 mg, 79%) which was obtained as a clear oil. The following characteristic values may be obtained by nuclear magnetic resonance spectroscopy:

^{1}H NMR (CD_3OD) δ: 6.97-7.37 m, 6.53 m, 5.45 t (J = 10.4 Hz), 5.33 t (J = 10.4 Hz), 5.24 dd (J = 7.8, 15.7 Hz), 4.94 dd (J = 6.9, 15.3 Hz), 3.86 bs, 3.48 bm, 2.91 dd (J = 7.9, 13.4 Hz), 2.67 dd (J = 6.8, 13.4 Hz), 2.64 m, 2.33 q (J = 10.5 Hz), 2.10 dd (J = 5.9, 12.1 Hz), 1.5 m, 1.41 s, 0.82 d (J = 6.0 Hz), 0.80 d (J = 6.5 Hz).

Example 11

Synthesis of Amide R013D

Acid R012D (127.3 mg, 190 μmol), *p*-nitrobenzyl methionine hydrochloride (obtained by HCl deprotection of 110 mg of *N*-BOC *p*-nitrobenzyl methionine, 290 μmol), HOBT (31.3 mg, 230 μmol), DCC (83.5 mg, 400 μmol), and NMM (25 μL, 230 μmol) were dissolved in anhydrous DMF (2.0 mL) and then stirred at room temp overnight. The reaction mixture was filtered, and the solid residue was washed well with ethyl acetate. The combined filtrates then were washed with water and phosphate buffer (pH 7.2). The aqueous phases were extracted with ethyl acetate, and the combined organic phases were dried once with brine, dried over $MgSO_4$, and concentrated to a yellow oil. Purification of the crude amide by FC, eluting with a 20-25% ethyl acetate-hexanes gradient, afforded amide R013D (165.8 mg, 93%) as a colorless foam. The following characteristic values may be obtained by nuclear magnetic resonance spectroscopy:

^{1}H NMR ($CDCl_3$) δ: 8.22 d (J = 8.7 Hz), 7.48 d (J = 8.7 Hz), 7.08-7.39 m, 6.15 bd, 5.55 t (J = 10.5 Hz), 5.41 t (J = 10.3 Hz), 5.31 dd (J = 7.0, 15.3 Hz), 5.22 ab quartet, 4.98 dd (J = 5.8, 15.4 Hz), 4.83 d (J = 5.7 Hz), 4.68 m, 4.52 bm, 4.09 bs, 3.33 q (J = 8.1 Hz), 3.06 dd (J = 7.9, 13.4 Hz), 2.70 dd (J = 6.7, 13.4 Hz), 2.59 m, 1.98 s, 1.42 s, 0.81 d (J = 6.7 Hz), 0.78 d (J = 6.7 Hz).

Example 12

Synthesis of Acid R014D

To a solution of *p*-nitrobenzyl ester R013D (88.8 mg, 98.9 μmol) in THF (1.5 mL) was added a solution of $Na_2S \cdot 9\,H_2O$ (126 mg, 0.52 mmol) in water (0.5 mL). The reaction mixture was stirred at room temp under N_2 for 2 h, whereupon it was quenched by addition of TFA (440 μL,

5.71 mmol). Solvents were removed under reduced pressure, and the residue was dissolved in methanol. Undissolved solid was removed by filtration, and the filtrate was purified by HPLC on C18 reverse phase columns, eluting with a gradient of 0.15% TFA in 5% acetonitrile-water to 0.15% TFA in acetonitrile. Acid **R014D** (48.8mg, 69%) was obtained as a colorless oil. The following characteristic values may be obtained by nuclear magnetic resonance spectroscopy:

^{1}H NMR (CD_3OD) δ: 7.09-7.39 m, 5.55 t, (J = 10.4 Hz), 5.34 t (J = 10.5 Hz), 5.20 dd (J = 6.8, 15.3 Hz), 4.93 m, 4.40 dd (J = 3.9, 9.4 Hz), 3.89 bs, 3.52 q (J = 8.2 Hz), 2.82 dd (J = 10.1, 12.8 Hz), 2.64 dd (J = 5.4, 13.3 Hz), 2.40 dd (J = 7.6, 11.8 Hz), 2.14 dd (J = 6.0, 12.2 Hz), 1.96 s, 1.66 m, 1.52 m, 085 d (J = 7.2 Hz), 0.83 d (J = 7.0 Hz).

Example 13

Synthesis of PD331

TFA (~3 mL) was added to a slurry of acid **R014D** (48.8 mg, 88.2 μmol) in Et_3SiH (1 mL) at room temp, and the solution was stirred for 5 min. **PD331** (27 mg, 68%) was obtained as a white solid after removal of solvents, purification of the residue by HPLC on C18 reverse phase columns (the elution gradient was 0.15% TFA in 5% acetonitrile-water to 0.15% TFA in acetonitrile), and lyophilization from acetonitrile-water. The following characteristic values may be obtained by nuclear magnetic resonance spectroscopy:

^{1}H NMR (CD_3OD) δ: 8.13 d (J = 8.3 Hz), 7.15-7.28 m, 5.79 dd (J = 7.9, 15.7 Hz), 5.64 t (J = 10.4 Hz), 5.42 t (J = 10.5 Hz), 5.37 dd (J = 8.0, 15.2 Hz), 4.45 m, 3.80 q (J = 6.6 Hz), 3.59 q (J = 8.3 Hz), 2.95 dd (J = 9.4, 13.2 Hz), 2.76 dd (J = 6.2, 10.8 Hz), 2.71 dd (J = 6.3,

12.9 Hz), 2.09 m, 1.99 s, 1.93 m, 1.65 m, 0.93 d (J = 6.8 Hz), 0.90 J = 6.8 Hz).

Example 14

Synthesis of Acrylate Ester R016D

$CrCl_2$ (17 g, 141 mmol) and then a solution of $Ni(COD)_2$ (193 mg, 0.7 mmol) in THF (~2 mL) were added to a solution of aldehyde **R015D** (21.1 g, 86 mmol) and *E*-3-iodoacrylate (30 g, 141 mmol) in THF (250 mL) in a dry box that was maintained with an inert atmosphere. Following the addition, a mild exotherm occurred, and the temperature of the mixture increased to approximately 50 - 60°C. The reaction mixture was stirred for an additional 14 h, at which time additional $CrCl_2$ (5.28 g, 43 mmol) and *E*-3-iodoacrylate (10 g, 47 mmol) were added. After an additional 16 h, $CrCl_2$ (5.28 g, 43 mmol) and $Ni(COD)_2$ (65 mg, 0.23 mmol) again were added. Twelve hours later, TLC monitoring (20% ethyl acetate-hexanes) indicated that the starting material was consumed.

The reaction then was diluted with saturated aqueous NH_4Cl (300 mL) and $CHCl_3$ (300 mL), and the resulting two-phase mixture was rapidly stirred overnight. The layers were separated, and the organic phase was rapidly stirred with saturated aqueous NH_4Cl (300 mL) for 2 h. The combined aqueous phases were extracted with $CHCl_3$ (2 x 200 mL). The combined organic phases were dried once with brine, further dried over Na_2SO_4, filtered, and concentrated to a crude oil. This oil was further purified several times with silica gel FC's. For the initial columns, elutions were performed with 10-30% ethyl acetate-hexanes gradients; for later columns 10-20% ether:CH_2Cl_2 gradients were used. Acrylate ester **R016D** (17.4 g, 61%) was obtained as a mixture of C.4 alcohols as a slightly impure yellow oil. From examination of the ^1H NMR spectrum, the α:β ratio appeared

to be approximately 1:2. The following characteristic values may be obtained by nuclear magnetic resonance spectroscopy:

^1H NMR ($CDCl_3$) δ: 6.99 bd (J = 14.0 Hz, β), 6.96 dd (J = 5.6, 15.6 Hz, α), 6.17 dd (J = 1.7, 15.5 Hz, β), 6.13 dd (J = 1.0, 15.4 Hz, α), 4.65 s (β), 4.61 t (J = 6.6 Hz, α), 4.50 bs (β), 4.48 t (J = 6.7 Hz, α), 3.75 s (β), 3.74 s (α), 3.15 dd (J = 6.2, 12.4 Hz), 2.91 d (J = 12.3 Hz, β), 2.71 d (J = 12.5 Hz α), 1.76 s, 1.74 s, 1.44 s.

Example 15

Synthesis of Mesylates R017D

Triethylamine (13.4 mL, 96.3 mmol) was added to a solution of alcohols R016D (19.1 g, 57.6 mmol) in CH_2Cl_2 (150 mL, at 0°C). Methanesulfonyl chloride (7 mL, 90 mmol) subsequently was added dropwise. The mixture was stirred for 20 min at 0°C, then the ice bath was removed, and the mixture was stirred an additional 30 min at ambient temperature. The reaction was quenched by addition of saturated aqueous NH_4Cl (400 mL), diluted with ethyl acetate (1 L), and shaken. The layers then were separated, and the organic layer was dried once with brine, further dried over Na_2SO_4, filtered, and then concentrated. The crude mesylate was purified by FC, eluting with a 0-30% ethyl acetate-hexane gradient affording mesylates R017D (22.0 g, 93%) as a yellow oil. The following characteristic values may be obtained by nuclear magnetic resonance spectroscopy:

^1H NMR ($CDCl_3$) δ: 7.08 dd (J = 6.3, 15.6 Hz, α), 6.93 bdd (J = 8.2, 14.8 Hz, β), 6.05 bd (J = 14.4 Hz, β), 5.59 bm (α), 5.43 t (J = 7.8 Hz), 3.75 s (α), 3.71 s (β), 3.20 dd

(J = 6.7, 12.9 Hz, α), 3.16 dd (J = 5.7, 12.7 Hz, β), 3.07 bm (α), 2.99 s, 2.96 bd (J = 12.7 Hz, β), 1.73 bs, 1.70 bs, 1.41 s.

Example 16

Synthesis of Olefinic Esters R018D

A 2 M solution of *i*-PrMgCl in THF (111 mL, 222 mmol) was added dropwise to a suspension of CuCN (20 g, 222 mmol) in THF (200 mL, at -40 °C). The reaction mixture turned black and became viscous. After the addition was complete, the mixture was warmed to 0°C, stirred for an additional 30 min, then recooled to -78°C. Then, $BF_3 \bullet OEt_2$ (31.5g, 222 mmol) was added, the reaction mixture was stirred for 5 min, and a solution of mesylates R018D (22 g, 53.7 mmol) in THF (40 mL) then was added by cannula. After 15 min, TLC (20% ethyl acetate-hexanes) indicated that the starting material had completely disappeared. The reaction was quenched with 1:1 saturated aqueous NH_4Cl:aqueous NH_4OH (50 mL), and the mixture was allowed to warm to ambient temperature. Additional saturated aqueous NH_4Cl (400 mL), NH_4OH (50 mL), and ethyl acetate (1 L) were added, and the mixture was vigorously stirred for 1 h. The layers were filtered through CELITE®, separated, and the aqueous layer was extracted with ethyl acetate (300 mL). The combined organic phases were washed with water (400 mL), dried once with brine (1 L), dried over Na_2SO_4, filtered through $MgSO_4$, and then concentrated. The crude product was purified by FC, eluting with a 5-10% ethyl acetate-hexanes gradient. Esters R018D (13.8 g, 71%) were obtained as a colorless oil as a mixture of C.2 isomers. The following characteristic values may be obtained by nuclear magnetic resonance spectroscopy:

^{1}H NMR ($CDCl_3$) δ: 5.66 m, 4.78 bm, 3.66 s, 3.25 dd (J = 5.6, 11.6 Hz, β), 3.24 dd (J = 5.9, 11.7 Hz, α), 2.66 m, 2.57 d (J = 11.7 Hz, β), 2.55 d (J = 11.8 Hz, α), 1.96 b sept (J = 6.7 Hz), 1.77 s, 1.74 s, 1.42 s (α), 1.41 s (β), 0.89 d (J = 6.5 Hz, α), 0.87 d (J = 8.0 Hz), 0.85 d (J = 6.5 Hz, β).

Example 17

Synthesis of Alcohol R019D

A 1 M solution of DIBAL in cyclohexane (76 mL, 76 mmol) was added to a solution of ester **R018D** (13.6 g, 38.0 mmol) in toluene (250 mL) stirring at room temp. The reaction was stirred for 15 min and then quenched by the addition of saturated sodium potassium tartrate (250 mL). The resulting heterogeneous mixture was stirred vigorously for 2 h at room temp, diluted with ethyl acetate (500 mL), and the organic layer then was separated, dried with brine, dried over Na_2SO_4, filtered through $MgSO_4$, and concentrated. The resulting crude mixture of alcohols was separated and purified by FC, eluting with a 5%-25% ethyl acetate-hexanes gradient to afford the α C.2 alcohol **R019D** (8.5 g, 68%) and the β C.2 alcohol isomer (3.6g, 29%). The following characteristic values may be obtained by nuclear magnetic resonance spectroscopy:

^{1}H NMR ($CDCl_3$) δ α-isomer: 5.67 dd (J = 6.3, 15.3 Hz), 5.39 dd (J = 9.3, 15.2 Hz), 4.83 bm, 3.65 m, 3.31 t (J = 10.1 Hz), 3.26 dd (J = 6.1, 11.7 Hz), 2.58 d (J = 11.7 Hz), 1.99 m, 1.77 bs, 1.74 s, 1.43 s, 0.89 d (J = 6.7 Hz), 0.85 d (J = 6.7 Hz).

^{1}H NMR ($CDCl_3$) δ β-isomer: 5.62 dd (J = 7.1, 15.2 Hz), 5.33 m, 4.73 bm, 3.64 dt (J = 5.4, 15.2 Hz), 3.32 t

(J = 10.4 Hz), 3.36 dd (J = 6.2, 11.8 Hz), 1.98 m, 1.73 bs, 1.43 s, 0.88 d (J = 6.7), 0.84 d (J = 6.7 Hz).

Example 18

Synthesis of Aldehyde R020D

The Dess-Martin Periodinane, 1,1,1,-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one, (5.4 g, 12.9 mmol) was suspended in diethyl ether (25 mL) under argon and stirred for 5 min. The ether was decanted, and the reagent was dried under a stream of argon for 10 min. The resulting solid was suspended in CH_2Cl_2 (25 mL), and then 4 Å molecular sieves (1 g) and *t*-butanol (956 mg, 12.9 mmol) were added. The mixture was stirred for 30 min, after which alcohol **R019D** (1.42 g, 4.31 mmol) was added. After 4 h, TLC monitoring (eluting with 20% ethyl acetate-hexanes) indicated that the reaction was complete. Diethyl ether (50 mL) was added, and the resulting suspension was filtered through CELITE®. The filtrate was washed with 10% $Na_2S_2O_3$ (30 mL), saturated aqueous $NaHCO_3$ (30 mL), and water, then dried with brine, dried over Na_2SO_4, filtered, and concentrated to an oil. The crude aldehyde was purified by FC, eluting with 10% ethyl acetate hexanes to afford aldehyde **R020D** (1.3 g, 92%) as a colorless oil. The following characteristic values may be obtained by nuclear magnetic resonance spectroscopy:

^1H NMR ($CDCl_3$) δ: 9.57 d (J = 2.7 Hz), 5.74 dd (J = 7.0, 15.3 Hz), 5.60 bm, 4.84 bm, 3.26 dd (J = 6.0, 11.8 Hz), 2.70 bm, 2.56 d (J = 11.8 Hz), 2.10 o (J = 6.9 Hz), 1.74 s, 1.42 s, 0.94 d (J = 6.7 Hz), 0.90 d (J = 6.6 Hz).

Example 19

Synthesis of Acrylate Ester R021D

$CrCl_2$ (1.5 g, 11.9 mmol) and Ni(COD)$_2$ (7.3 mg,

0.026 mmol) were added sequentially to a solution of aldehyde R020D (1.3 g, 3.97 mmol) and E-3-iodoacrylate (2.5 g, 11.9 mmol) in THF (250 mL) in a dry box maintained with an inert atmosphere. The reaction mixture was stirred for 14 h, at which time TLC monitoring (20% ethyl acetate-hexanes) indicated that the starting material had been consumed.

The reaction was diluted with saturated aqueous NH_4Cl (100 mL) and stirred for 1 h at room temp. After dilution with $CHCl_3$ (100 mL) followed by vigorous mixing, the resulting emulsion was filtered through CELITE®. The layers were separated, and the organic phase was dried once with brine, dried over Na_2SO_4, filtered, and concentrated to a crude oil. The crude oil was purified by FC, eluting with 20% ethyl acetate-hexanes. Acrylate ester R021D (1.13 g, 68%) was obtained as a mixture of C.4 epimeric alcohols. The following characteristic values may be obtained by nuclear magnetic resonance spectroscopy:

^1H NMR ($CDCl_3$) δ: 6.97 dd (J = 4.7, 15.6 Hz), 6.01 dd (J = 1.4, 15.6 Hz), 5.70 dd (J = 6.5, 15.3 Hz), 5.30 m, 4.81 bm, 4.38 m, 3.26 dd (J = 6.2, 11.8 Hz), 2.55 bd (J = 11.9 Hz), 2.02 m, 1.73 s, 1.43 s, 0.95 d (J = 6.7 Hz), 0.87 d (J = 6.1 Hz).

Example 20

<u>Synthesis of Diene Ester R022D</u>

Triethylamine (604 μL, 4.34 mmol) was added to a solution of alcohols R021D (1.12 g, 2.71 mmol) in CH_2Cl_2 (15 mL at 0°C). Methanesulfonyl chloride (314 μL, 4.06 mmol) then was added dropwise. The mixture was stirred for 20 min at 0°C, the ice bath then was removed, and the mixture was stirred at ambient temperature for approximately 30 min. At that point, TLC (eluting with 20% diethyl ether-

CH_2Cl_2) indicated complete disappearance of starting material. The reaction was quenched by the addition of saturated aqueous NH_4Cl, then diluted with ethyl acetate, and shaken. The layers were separated, and the organic layer was dried once with brine, dried over Na_2SO_4, filtered, and then concentrated. The crude mesylate was used immediately for the following S_N2' displacement.

A 2.0 M solution of benzyl magnesium chloride in THF (5.4 mL, 10.8 mmol) was added dropwise to a suspension of CuCN in THF stirring at -40°C. After the addition was complete, the pale yellow solution was warmed to 0°C and stirred an additional 30 min. At that point the solution was gray. It then was cooled to -78°C, $BF_3{\bullet}OEt_2$ (1.3 mL, 10.8 mmol) added, and the solution was stirred an additional 10 min. Next a solution of the crude mesylate (described above, ≤2.71 mmol) dissolved in THF (5 mL), was added. This addition was followed by a rinse with THF (5 mL), and the resulting reaction mixture was stirred for 1 h at -78°C. The reaction was then quenched by the addition of a mixture of NH_4OH (10 mL) and saturated aqueous NH_4Cl (10 mL). The mixture was warmed to ambient temperature, and diluted with ethyl acetate and more NH_4Cl solution (50 mL). The aqueous layer was separated and extracted with ethyl acetate, and the combined organic layers were washed with water, dried with brine, dried over Na_2SO_4, filtered, and concentrated to a crude oil. Purification by FC, eluting with 3-10% ethyl acetate-hexanes, afforded the major β diene ester R022D (478 mg, 36%, isomer) and its C.2 minor isomer (333 mg, 25%). The following characteristic values may be obtained by nuclear magnetic resonance spectroscopy:

^1H NMR ($CDCl_3$) δ C.2 β isomer: 7.25 m, 7.12 m, 5.45 m, 4.72 bm, 3.62 q (J = 8.7 Hz), 3.60 s, 3.21 dd (J = 6.1, 11.6 Hz),

3.03 dd (J = 8.0, 13.6 Hz), 2.76 dd (J = 6.7, 13.6 Hz), 2.70 q (J = 8.3 Hz), 2.43 (J = 11.7 Hz), 1.78 s, 1.76 s, 1.55 oct (J = 6.8 Hz), 1.43 s, 0.87 d (J = 6.6 Hz), 0.82 d (J = 6.7 Hz).

^{1}H NMR ($CDCl_3$) δ C.2 α isomer: 7.25 m, 7.15 m, 5.45 m, 4.78 bm, 3.62 s, 3.31 m, 3.26 dd (J = 6.5, 12.0 Hz), 3.07 dd (J = 7.8, 13.6 Hz), 2.80 dd (J = 7.5, 13.7 Hz), 2.54 d (J = 11.6 Hz), 2.42 m, 1.835, 1.77 s, 1.56 oct (J = 6.7 Hz), 1.45 s, 0.79 d (J = 6.8 Hz).

Example 21

Synthesis of Acid R023D

A suspension of ester **R022D** (316 mg, 0.651 mmol) and LiOH (78 mg, 3.25 mmol) in a mixture of dioxane (2 mL) and water (2 mL) was stirred at ambient temperature overnight. The pH of the mixture was decreased to pH 2 with 0.1 N HCl, and the mixture then was extracted several times with ethyl acetate. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to acid **R023D** (301 mg, 98%), which was obtained as a clear oil. The following characteristic values may be obtained by nuclear magnetic resonance spectroscopy:

^{1}H NMR ($CDCl_3$) δ: 7.26 m, 7.17 m, 5.45 m, 5.42 m, 4.70 bm, 3.62 q (J = 7.7 Hz), 3.21 dd (J = 6.0, 11.6 Hz), 3.06 dd (J = 7.7, 13.7 Hz), 2.78 dd (J = 6.9, 13.6 Hz), 2.69 m, 2.42 d (J = 11.5 Hz), 1.77 s, 1.75 s, 1.56 oct (J = 6.8 Hz), 1.43 s, 0.86 d (J = 6.6 Hz), 0.83 d (J = 6.7 Hz).

Example 22

Synthesis of PNB Ester R024D

A solution of NMM (60 µL, 0.54 mmol) was added to a solution of acid **R023D** (245 mg, 0.517 mmol), EDC (119 mg, 0.62 mmol), HOBT (73 mg, 0.54 mmol), and methionine

p-nitrobenzyl ester hydrochloride (199 mg, 0.62 mmol) in DMF (4 mL). The resulting solution was stirred overnight at ambient temperature. The reaction mixture was diluted with ethyl acetate, washed with water (50 mL), dried twice with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated to a crude oil. Purification by FC, eluting with 20-30% ethyl acetate-hexanes, afforded pure PNB ester **R024D** (340 mg, 89%) as a colorless oil. The following characteristic values may be obtained by nuclear magnetic resonance spectroscopy:

^{1}H NMR ($CDCl_3$) δ: 8.23 d (J = 8.7 Hz), 7.49 d (J = 8.7 Hz), 7.25 m, 7.18 m, 6.14 bs, 5.50 m, 4.75 bm, 4.70 dt (J = 4.8, 7.5 Hz), 3.41 dt (J = 6.4, 8.9 Hz), 3.23 dd (J = 6.0, 11.6 Hz), 3.08 (J = 8.4, 13.4 Hz), 2.73 dd (J = 6.1, 13.4 Hz), 2.67 q (J = 7.9 Hz), 2.46 d (J = 11.7 Hz), 2.20 m, 2.1 m, 1.98 s, 1.84 m, 1.79 s, 1.76 s, 1.57 oct (J = 6.7 Hz), 1.44 s, 0.87 d (J = 6.2 Hz), 0.83 d (J = 6.6 Hz).

Example 23

<u>Synthesis of Acid **R025D**</u>

A solution of $Na_2S{\cdot}9\ H_2O$ (1.67 g, 6.95 mmol) in water (5 mL) to a solution of PNB ester **R024D** (1.03 g, 1.39 mmol) in THF (10 mL), and the resulting mixture was stirred for 1 h 45 min at ambient temperature. The reaction was quenched by addition of 1.2 mL TFA, stirred for 15 min, and the solvents were removed under vacuum. The residue was dissolved in methanol and purified by reverse phase HPLC, eluting with 0.15% TFA in 5% acetonitrile-water to 0.15% TFA in acetonitrile to yield acid **R025D** (797 mg, 95%). The following characteristic values may be obtained by nuclear magnetic resonance spectroscopy:

^{1}H NMR (CD_3OD) δ: 7.18 m, 7.10 m, 5.59 dd (J = 7.0, 15.2 Hz), 5.51 t (J = 10.4 Hz), 5.41 bm, 5.34 t (J = 10.4 Hz), 4.90 bs, 4.71 bm, 4.36 dd (J = 4.0, 9.3 Hz), 3.55 q (J = 4.7 Hz), 3.21 dd (J = 6.1, 11.8 Hz), 2.85 dd (J = 8.6, 14.9 Hz), 2.62 dd (J = 5.3, 13.2 Hz), 2.44 d (J = 11.8 Hz), 1.99 s, 1.85 m, 1.71 s, 1.68 s, 1.66 m, 1.37 s, 1.50 oct (J = 6.9 Hz), 1.37 s, 0.86 d (J = 6.3 Hz), 0.82 d (J = 6.7 Hz).

Example 24

Synthesis of Disulfide R026D

A solution of thiazolidine R025D (250 mg, 0.411 mmol) in acetic acid (0.6 mL), DMF (2.0 mL), and water (1.0 mL) was cooled to 0°C for 15 min. MeO_2CSCl (45 μL, 0.493 mmol) was added dropwise to this mixture. After stirring for 30 min further at 0°C, analysis by reverse phase HPLC (eluting with 0.15% TFA in 5% acetonitrile-water to 0.15% TFA in acetonitrile over 30 min) showed complete consumption of starting material. Solvents were removed under vacuum, and the residue was purified by reverse phase HPLC. Disulfide R026D (244 mg, 91%) was obtained as a colorless oil. The following characteristic values may be obtained by nuclear magnetic resonance spectroscopy:

^{1}H NMR (CD_3OD) δ: 7.24 m, 7.17 m, 5.58 t (J = 10.3 Hz), 5.54 dd (J = 8.7, 16.6 Hz), 5.39 t (J = 10.4 Hz), 5.33 dd (J = 6.6, 15.4 Hz), 4.42 m, 4.21 m, 2.87 s, 3.55 m, 2.89 m, 2.72 dd (J = 5.9, 13.2 Hz), 2.03 m, 1.98 s, 1.93 m, 1.71 m, 1.57 oct (J = 6.7 Hz), 1.42 s, 0.89 d (J = 6.7 Hz), 0.86 d (J = 6.7 Hz).

Example 25

Synthesis of Thiol R027D

A solution of n-Bu_3P (0.97 mL, 3.94 mmol) was added dropwise to a solution of disulfide R026D (863 mg, 1.32 mmol) in THF (30 mL) containing water (3 mL, ~166 mmol) at 0°C. After 18 min, analytical reverse phase HPLC (eluting with 0.15% TFA in 5% acetonitrile water to 0.15% TFA in acetonitrile over 30 min) indicated complete consumption of the starting material. The reaction mixture was loaded directly onto a preparative reverse phase HPLC column, and then purified. Thiol R027D (681 mg, 92%) was obtained as a clear oil. The following characteristic values may be obtained by nuclear magnetic resonance spectroscopy:

^1H NMR (CD_3OD) δ: 7.25 m, 7.17 m, 5.58 t (J = 10.4 Hz), 5.52 dd (J = 9.1, 16.8 Hz), 5.40 (J = 10.4 Hz), 5.29 dd (J = 6.7, 15.5 Hz), 4.43 m, 4.03 m, 3.58 q (J = 8.3 Hz), 2.90 m, 2.71 dd (J = 5.9, 13.2 Hz), 2.58 m, 2.03 m, 1.98 s, 1.91 m, 1.71 m, 1.58 oct (J = 6.8 Hz), 1.42 s, 0.89 d (J = 6.7 Hz), 0.86 d (J = 6.8 Hz).

Example 26

Synthesis of Compound PD331

A solution of N-BOC protected thiol R027D (681 mg, 1.2 mmol) in CH_2Cl_2 (10 mL) and TFA (10 mL) was stirred at 0°C for 55 min. The mixture was worked up and purified as described above, affording pure analog PD331 (354 mg, 80%).

Example 27

Synthesis of Amide R028D

A mixture of acid R023D (80 mg, 0.169 mmol), HCl•MeNHOMe (20 mg, 0.203 mmol), EDC (49 mg, 0.254 mmol), and NMM (19 mL, 0.169 mmol) in 3 mL CH_2Cl_2 was stirred at ambient temperature for 16 h. The resulting mixture was

diluted with ethyl acetate (30 mL) and water (15 mL), transferred to a separatory funnel, and then shaken. The organic layer was washed with water, dried with brine, dried over Na_2SO_4, filtered, and concentrated. The crude oil was purified by FC eluting with 15% ethyl acetate-hexanes to afford the desired amide **R028D** (68 mg, 78%) as a colorless oil. The following characteristic values may be obtained by nuclear magnetic resonance spectroscopy:

^1H NMR ($CDCl_3$) δ: 7.25 m, 7.17 m, 5.60 t (J = 10.2 Hz), 5.56 m, 5.47 m, 5.40 t (J = 10.4 Hz), 4.77 b m, 4.08 b m, 3.30 s, 3.25 (J = 6.1, 11.6 Hz), 3.10 dd (J = 8.7, 12.1 Hz), 3.08 s, 2.76 q (J = 8.1 Hz), 2.66 dd (J = 5.2, 13.2 Hz), 2.50 d (J = 11.6 Hz), 1.81 s, 1.77 s, 1,57 oct (J = 6.9 Hz), 1.45 s, 0.87 d (J = 6.7 Hz), 0.83 d (J = 6.7 Hz).

Example 28

Synthesis of Aldehyde **R029D**

Lithium aluminum hydride (6 mg, 0.16 mmol) **was** added to a solution of amide **R028D** (68 mg, 0.13 mmol) in diethyl ether (5 mL) maintained at 0°C. After stirring for 30 min, the resulting reaction mixture was quenched with saturated aqueous sodium potassium tartrate and stirred an additional 30 minutes. The layers were separated and the aqueous layer extracted with ethyl acetate. The combined organic layers were dried with brine, dried over Na_2SO_4, filtered, and concentrated to the crude aldehyde, **R029D** used directly in the next reaction.

Example 29

Synthesis of Amine **R030D**

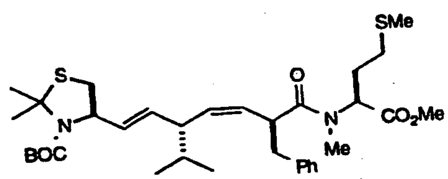
Sodium cyanoborohydride (41 mg, 0.195 mmol) was added to a solution of the hydrochloride salt of methionine *p*-nitrobenzyl ester (64 mg, 0.195 mmol) and crude aldehyde **R029D** ($\leq$ 0.13 mmol) in ethanol (5 mL). The resulting mixture

was stirred at ambient temperature overnight and then diluted with ethyl acetate and water. The organic layer was dried with brine, dried over Na_2SO_4, filtered, and concentrated to a crude oil. After purification by FC eluting with 20% ethyl acetate-hexanes, amine **R030D** (45 mg, 47%) was obtained as a white solid. The following characteristic values may be obtained by nuclear magnetic resonance spectroscopy:

^1H NMR ($CDCl_3$) δ: 8.24 d (J = 8.8 Hz), 7.51 d (J = 8.7 Hz), 7.25 t (J = 7.6 Hz), 7.16 t (J = 6.8 Hz), 7.11 d (J = 7.6 Hz), 5.49 m, 5.42 t (J = 10.4 Hz), 5.25 d (J = 13.3 Hz), 5.23 ab q, 5.18 t (J = 10.3 Hz), 3.37 dd (J = 5.6, 7.8 Hz), 3.21 dd (J = 5.9, 11.6 Hz), 2.83 m, 2.73 q (J = 8.1 Hz), 2.54 m, 2.40 m, 2.04 s, 1.89 m, 1.75 s, 1.54 m, 1.44 s, 0.88 d (J = 6.4 Hz), 0.86 (J = 6.6 Hz).

Example 30

Synthesis of Ester R031D



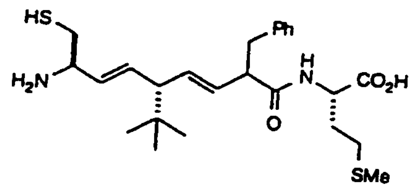
In a procedure similar to that used for the preparation of PNB ester **R024D** above, acid **R023D** (93 mg, 0.203 mmol) and *N*-methyl methionine methyl ester hydrochloride (36 mg,0.203 mmol) were coupled to afford ester **R031D** (24 mg, 19%) as a yellow oil. The following characteristic values may be obtained by nuclear magnetic resonance spectroscopy:

^1H NMR ($CDCl_3$) δ: 7.26 m, 7.18 m, 5.61 m, 5.48 m, 5.15 dd

(J = 4.4, 10.4 Hz), 4.64 dt (J = 5.1, 7.3 Hz), 3.64 s, 3.26 dd (J = 6.1, 7.9 Hz), 3.10 dd (J = 10.0, 13.3 Hz), 2.75 s, 2.2 m, 2.11 m, 2.02 s, 1.6 m, 1.44 s, 0.88 d (J = 6.9 Hz), 0.86 d (J = 8.1 Hz).

Example 31

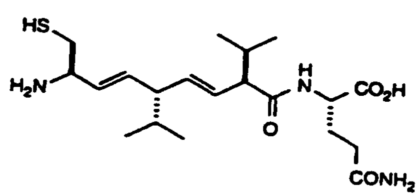
Compound PD012



^1H NMR (CD_3OD) δ: 8.22 d (J = 8 Hz), 7.13 - 7.26 m, 6.02 dd (J = 7.3, 15.5 Hz), 5.65 dd (J = 8.7, 15.3 Hz), 5.50 dd (J = 7.9, 15.4 Hz), 5.43 ddd (J = 1.2, 8.0, 15.6 Hz), 4.46 m, 3.82 q (J = 7.3 Hz), 2.98 dd (J = 11.8, 13.3 Hz), 2.81 dd (J = 6.4, 15.3 Hz), 2.75 m, 2.53 t (J = 7.7 Hz), 2.16 ddd (J = 2.6, 8.7, 13.4 Hz), 2.05 m, 1.98 s, 1.73 m, 0.85 s.

Example 32

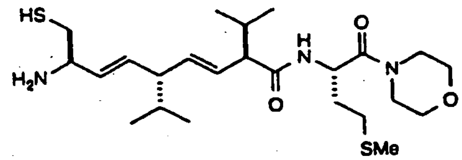
Compound PD022



^1H NMR (CD_3OD) δ: 8.35 d (J = 8 Hz), 5.91 dd (J = 8.1, 15.5 Hz), 5.57 dd (J = 7.3, 15.5 Hz), 5.48 dd (J = 8.9, 15.4 Hz), 5.42 dd (J = 7.8, 15.4 Hz), 4.35 dd (J = 5.3, 8.7 Hz), 3.84 q (J = 7.1 Hz), 2.80 dd (J = 6.4, 14.3 Hz), 2.76 dd (J = 6.1, 14.1 Hz), 2.6 m, 2.27 m, 2.1 m, 1.95 m, 1.7 m, 0.94 d (J = 6.6 Hz), 0.91 d (J = 6.5 Hz), 0.90 d (J = 6.7 Hz), 0.88 d (J = 6.9 Hz).

Example 33

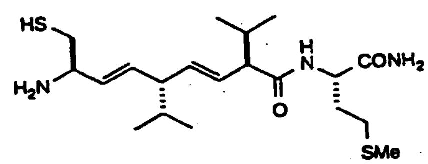
Compound PD032



^1H NMR (CD_3OD) δ: 8.29 d (J = 8.0 Hz), 5.92 dd (J = 8.2, 15.6 Hz), 5.57 dd (J = 7.6, 15.5 Hz), 5.46 dd (J = 9.1, 15.4 Hz), 5.43 dd (J = 8.1, 15.5 Hz), 4.99 dt (J = 5.1, 8.4 Hz), 3.84 q (J = 7.5 Hz), 3.6 - 3.75 m, 3.52 m, 2.81 dd (J = 6.4, 14.0 Hz), 2.74 (J = 6.2, 14.0 Hz), 2.4 - 2.65 m, 2.06 s, 1.90 m, 1.71 o (J = 6.6 Hz), 0.91 d (J = 6.4 Hz), 0.90 d (J = 5.9 Hz), 0.89 d (J = 6.6 Hz), 0.86 d (J = 6.8 Hz).

Example 34

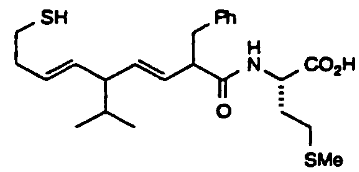
Compound PD042



^1H NMR (CD_3OD) δ: 8.12 d (J = 7.9 Hz), 5.92 dd (J = 8.1, 15.5 Hz), 5.57 dd (J = 7.6, 15.4 Hz), 5.46 dd (J = 9.4, 14.9 Hz), 5.43 dd (J = 7.7, 15.2 Hz), 4.48 m, 3.84 q (J = 7.3 Hz), 2.81 dd (J = 6.4, 14.5 Hz), 2.74 dd (J = 6.1, 14.5 Hz), 2.59 m, 2.48 m, 2.06 s, 2.05 m, 1.90 m, 1.71 o (J = 6.7 Hz), 0.91 d (J = 6.0 Hz), 0.91 (J = 6.5 Hz), 0.90 d (J = 6.1 Hz), 0.87 d (J = 6.7 Hz).

Example 35

Compound PD052

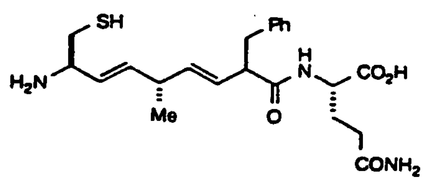


Isomer I

^{1}H NMR (CD_3OD) δ: 8.12 d (J = 8.2 Hz), 7.13 - 7.25 m, 5.52 dd (J = 6.5, 14.8 Hz), 5.47 dd (J = 7.1, 15.2 Hz), 5.40 dd (J = 7.7, 15.4 Hz), 5.26 dt (J = 7.2, 14.3 Hz), 4.44 dt (J = 3.7, 9.1 Hz), ~ 3.30 m, 2.98 dd (J = 9.3, 13.3 Hz), 2.73 dd (J = 6.3, 13.3 Hz), 2.50 (J = 7.2 Hz), 2.42 (J = 6.9 Hz), 2.28 (J = 7.0 Hz), ~2.1 m, 1.98 s, ~1.32 m, 1.57 o (J = 6.7 Hz), 0.83 d (J = 6.8 Hz), 0.83 d (J = 6.7 Hz).

Example 36

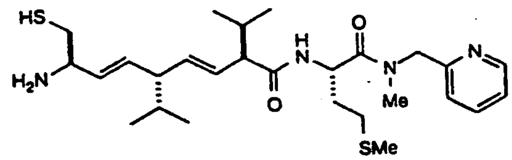
Compound PD062



^{1}H NMR (CD_3OD) δ: 8.26 d (J = 8 Hz), 7.05 - 7.3 m, 5.62 dd (J = 8.0, 14.1 Hz), 5.55 dd (J = 10.0, 14.1 Hz), 4.28 m, 3.71 m, 3.01 m, 2.78 m, 2.35m, 2.23 m, 1.65 - 2.12 m, 0.99 d (J = 7.2 Hz).

Example 37

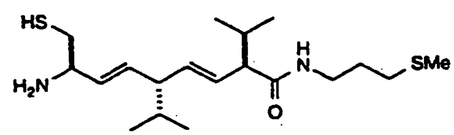
Compound PD072



^1H NMR (CD_3OD) δ: 8.63 d (J = 5.0 Hz), 8.16 t (J = 7.2 Hz), 7.62 d (J = 7.7 Hz), 7.50 m, 5.92 dd (J = 7.9, 15.3 Hz), 5.57 dd (J = 7.6, 15.3 Hz), 5.47 dd (J = 9.9, 16.5 Hz), 5.43 dd (J = 8.1, 15.5 Hz), 5.02 m, 4.99 d (J = 14.5 Hz), 4.64 d (J = 16.1 Hz), 3.84 m, 3.32 s, 2.8 - 3.0 m, 2.09 s, 1.05 m, 1.70 m, 0.91 d (J = 6.7 Hz), 0.90 d (J = 6.6 Hz), 0.86 d (J = 6.9 Hz), 0.83 d (J = 6.7 Hz).

Example 38

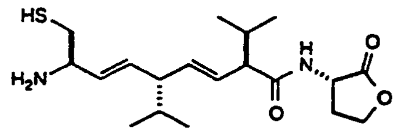
Compound PD082



^1H NMR (CD_3OD) δ: 8.07 t (J = 5.2 Hz), 5.50 dd (J = 8.7, 15.2 Hz), 5.41 dd (J = 9.1, 15.3 Hz), 3.63 m, 3.26 m, 3.06 dd (J = 6.7, 10.7 Hz), 2.73 dd (J = 9.3, 10.5 Hz), 2.47 m, 2.04 s, 2.00 m, 1.90 m, 1.6 - 1.8 m, 0.92 d (J = 6.7 Hz), 0.89 d (J = 6.7 Hz), 0.87 d (J = 6.8 Hz), 0.83 d (J = 6.8 Hz).

Example 39

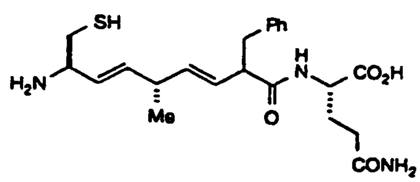
Compound PD092



^{1}H NMR (CD_3OD) δ: 8.54 d (J = 7.7 Hz), 5.92 dd (J = 8.0, 15.5 Hz), 5.56 dd (J = 7.5, 15.4 Hz), 5.46 dd (J = 9.5, 14.8 Hz), 5.42 dd (J = 8.2, 15.4 Hz), 4.54 m, 4.43 dt (J = 1.9, 9.0 Hz), 4.13 m, 3.84 q (J = 7.2 Hz), 2.82 dd (J = 6.4, 14.5 Hz), 2.74 dd (J = 6.1, 14.5 Hz), 2.60 q (J = 7.0 Hz), 2.52 m, 2.23 m, 1.93 m, 1.70 o (J = 6.7 Hz), 0.96 d (J = 6.6 Hz), 0.92 d (J = 6.5 Hz), 0.90 d (J = 6.4 Hz), 0.90 d (J = 6.8 Hz).

Example 40

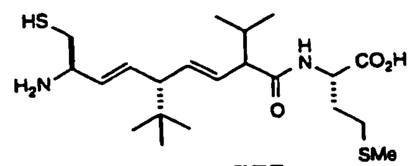
Compound PD102



^{1}H NMR (CD_3OD) δ: 8.23 d (J = 7.9 Hz), 7.12 - 7.24 m, 5.61 dd (J = 7.8, 15.5 Hz), 5.51 dd (J = 7.8, 15.5 Hz), 4.33 m, 3.73 m, 3.36 m, 3.05 m, 2.77 m, 2.40 m, 1.69 - 2.35 m, 1.59 q (J = 11.2 Hz), 1.04 d (J = 6.8 Hz).

Example 45

Compound PD152

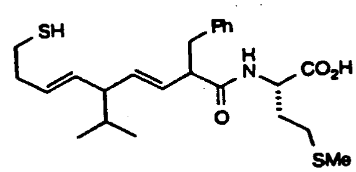


Isomer III

^{1}H NMR (CD$_3$OD) δ: 8.31 d (J = 8.0 Hz), 6.01 dd (J = 8.6, 15.5 Hz), 5.65 dd (J = 8.4, 15.3 Hz), 5.46 dd (J = 9.0, 15.5 Hz), 5.42 dd (J = 8.3, 15.2 Hz), 4.53 m, 3.85 q (J = 6.7 Hz), 2.81 dd (J = 6.5, 14.1 Hz), 2.75 dd (J = 6.1, 14.1 Hz), 2.51 - 2.61 m, 2.45 dt (J = 13.4, 7.9 Hz), 2.1 m, 2.06 s, 0.93 d (J = 6.6 Hz), 0.90 s, 0.86 d (J = 6.7 Hz) (an epimer of PD142).

Example 46

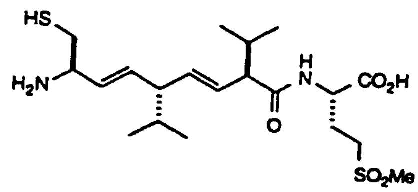
Compound PD162



^{1}H NMR (CD$_3$OD) δ: 8.23 d (J = 8.0 Hz), 7.11 - 7.24 m, 5.43 dd (J = 7.9, 15.5 Hz), 5.36 dd (J = 7.3, 15.3 Hz), 5.33 dd (J = 7.6, 15.4 Hz), 5.13 dt (J = 14.5, 7.2 Hz), 4.52 m, 3.27 q (J = 7.5 Hz), 3.04 dd (J = 6.7, 13.6 Hz), 2.73 dd (J = 8.3, 13.6 Hz), 2.36 - 2.52 m, 2.24 q (J = 7.0 Hz), 2.09 m, 2.04 s, ~ 1.9 m, 1.53 o (J = 6.7 Hz), 0.79 d (J = 6.7 Hz), 0.788 (J = 6.8 Hz).

Example 47

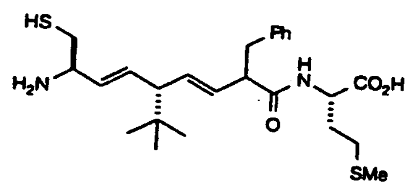
Compound PD172



^1H NMR (CD_3OD) δ: 8.38 d (J = 7.6 Hz), 5.87 dd (J = 8.2, 15.5 Hz), 5.55 dd (J = 7.4, 15.5 Hz), 5.45 dd (J = 9.1, 15.4 Hz), 5.39 dd (J = 7.8, 15.2 Hz), 4.51 m, 3.80 m, 3.60 m, 3.15 m, 3.00 m, 2.92 s, 2.78 dd (J = 6.3, 14.2 Hz), 2.70 dd (J = 5.9, 14.1 Hz), 2.56 m, 2.33 m, 2.09 m, 1.89 m, 1.68 o (J = 6.7 Hz), 0.89 d (J = 5.8 Hz), 0.88 d (J = 6.7 Hz), 0.85 d (J = 5.5 Hz), 0.85 d (J = 6.8 Hz).

Example 48

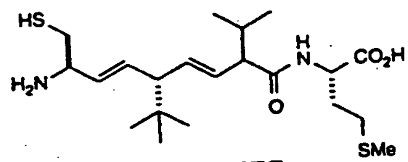
Compound PD182



^1H NMR (CD_3OD) δ: 8.27 d (J = 8.0 Hz), 7.12 - 7.25 m, 5.90 dd (J = 8.7, 15.5 Hz), 5.57 dd (J = 7.7, 15.4 Hz), 5.48 dd (J = 8.0, 15.4 Hz), 5.32 dd (J = 7.8, 15.4 Hz), 4.49 m, 3.81 q (J = 6.6 Hz), 3.32 dd (J = 8.1, 15.7 Hz), 2.68 - 2.82 m, 2.35 - 2.51 m, 2.1m, 2.04 s, 1.90 m, 0.83 s.

Example 45

Compound PD152

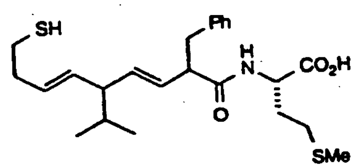


Isomer III

^{1}H NMR (CD_3OD) δ: 8.31 d (J = 8.0 Hz), 6.01 dd (J = 8.6, 15.5 Hz), 5.65 dd (J = 8.4, 15.3 Hz), 5.46 dd (J = 9.0, 15.5 Hz), 5.42 dd (J = 8.3, 15.2 Hz), 4.53 m, 3.85 q (J = 6.7 Hz), 2.81 dd (J = 6.5, 14.1 Hz), 2.75 dd (J = 6.1, 14.1 Hz), 2.51 - 2.61 m, 2.45 dt (J = 13.4, 7.9 Hz), 2.1 m, 2.06 s, 0.93 d (J = 6.6 Hz), 0.90 s, 0.86 d (J = 6.7 Hz) (an epimer of PD142).

Example 46

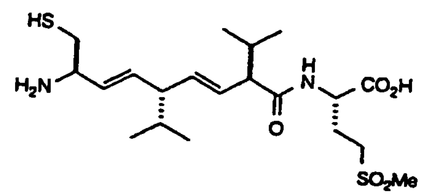
Compound PD162



^{1}H NMR (CD_3OD) δ: 8.23 d (J = 8.0 Hz), 7.11 - 7.24 m, 5.43 dd (J = 7.9, 15.5 Hz), 5.36 dd (J = 7.3, 15.3 Hz), 5.33 dd (J = 7.6, 15.4 Hz), 5.13 dt (J = 14.5, 7.2 Hz), 4.52 m, 3.27 q (J = 7.5 Hz), 3.04 dd (J = 6.7, 13.6 Hz), 2.73 dd (J = 8.3, 13.6 Hz), 2.36 - 2.52 m, 2.24 q (J = 7.0 Hz), 2.09 m, 2.04 s, ~ 1.9 m, 1.53 o (J = 6.7 Hz), 0.79 d (J = 6.7 Hz), 0.788 (J = 6.8 Hz).

Example 47

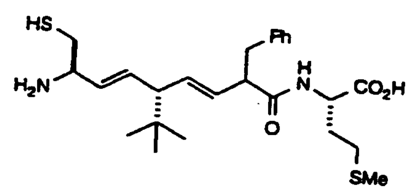
Compound PD172



^{1}H NMR (CD_3OD) δ: 8.38 d (J = 7.6 Hz), 5.87 dd (J = 8.2, 15.5 Hz), 5.55 dd (J = 7.4, 15.5 Hz), 5.45 dd (J = 9.1, 15.4 Hz), 5.39 dd (J = 7.8, 15.2 Hz), 4.51 m, 3.80 m, 3.60 m, 3.15 m, 3.00 m, 2.92 s, 2.78 dd (J = 6.3, 14.2 Hz), 2.70 dd (J = 5.9, 14.1 Hz), 2.56 m, 2.33 m, 2.09 m, 1.89 m, 1.68 o (J = 6.7 Hz), 0.89 d (J = 5.8 Hz), 0.88 d (J = 6.7 Hz), 0.85 d (J = 5.5 Hz), 0.85 d (J = 6.8 Hz).

Example 48

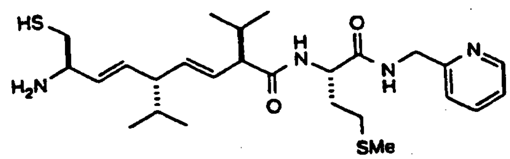
Compound PD182



^{1}H NMR (CD_3OD) δ: 8.27 d (J = 8.0 Hz), 7.12 - 7.25 m, 5.90 dd (J = 8.7, 15.5 Hz), 5.57 dd (J = 7.7, 15.4 Hz), 5.48 dd (J = 8.0, 15.4 Hz), 5.32 dd (J = 7.8, 15.4 Hz), 4.49 m, 3.81 q (J = 6.6 Hz), 3.32 dd (J = 8.1, 15.7 Hz), 2.68 - 2.82 m, 2.35 - 2.51 m, 2.1m, 2.04 s, 1.90 m, 0.83 s.

Example 49

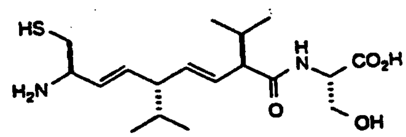
Compound PD192



^1H NMR (CD_3OD) δ: 8.70 d (J = 5.3 Hz), 8.39 dt (J = 0.9, 7.7 Hz), 7.89 d (J = 8.1 Hz), 7.81 t (J = 6.2 Hz), 5.92 dd (J = 8.4, 15.6 Hz), 5.56 dd (J = 7.7, 16.1 Hz), 5.47 dd (J = 9.8, 16.2 Hz), 5.42 dd (J = 7.9, 15.7 Hz), 4.76 d (J = 16.8 Hz), 4.60 d (J = 16.8 Hz), 4.47 dd (J = 5.3, 9.1 Hz), 3.84 q (J = 7.4 Hz), 2.80 dd (J = 6.5, 12.9 Hz), 2.74 dd (J = 6.1, 12.9 Hz), 2.42 - 2.66 m, 2.07 s, 1.94 m, 1.70 o (J = 6.7 Hz), 0.91 d (J = 6.9 Hz), 0.89 d (J = 6.9 Hz), 0.86 d (J = 6.8 Hz), 0.83 d (J = 6.7 Hz).

Example 50

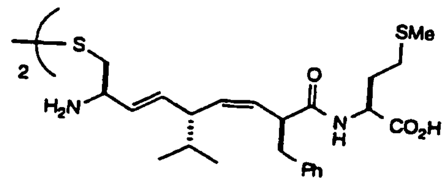
Compound PD202



^1H NMR (CD_3OD) δ: 8.08 d (J = 8.3 Hz), 5.92 dd (J = 9.2, 15.6 Hz), 5.57 dd (J = 7.3, 15.5 Hz), 5.49 dd (J = 9.0, 15.4 Hz), 5.43 dd (J = 8.0, 15.2 Hz), 4.46 dd(J = 4.5, 9.2 Hz), 3.89 dd (J = 5.0, 11.1 Hz), ~ 3.8 m, 3.76 dd (J = 4.1, 11.1 Hz), ~ 3.65 m, 2.55 - 2.90 m, 1.95 m, 1.70 m, 0.95 d (J = 6.5 Hz), 0.91 d (J = 6.7 Hz), 0.90 d (J = 6.2 Hz), 0.89 d (J = 6.1 Hz).

Example 51

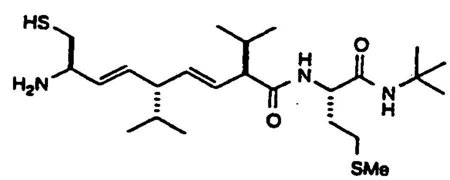
Compound PD212



^{1}H NMR (CD_3OD) δ: 8.10 d (J = 8.6 Hz), 7.13 - 7.30 m, 5.79 dd (J = 7.8, 15.4 Hz), 5.64 t (J = 10.4 Hz), 5.41 dd (J = 8.1, 15.2 Hz), 5.38 t (J = 10.6 Hz), 4.43 m, 4.00 q (J = 6.6 Hz), 3.58 dt (J = 5.8, 9.2 Hz), 3.10 dd (J = 6.0, 13.9 Hz), 2.94 m, 2.70 dd (J = 5.6, 13.2 Hz), 2.05 m, 1.98 s, 1.90 m, 1.70 m, 1.63 o (J = 6.9 Hz), 0.92 d (J = 6.6 Hz), 0.89 (6.7 Hz).

Example 52

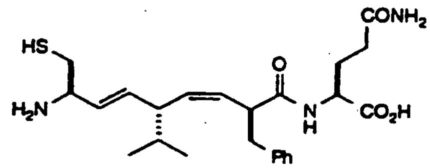
Compound PD222



^{1}H NMR (CD_3OD) δ: 8.07 d (J = 8 Hz), 5.92 dd (J = 8.0, 15.1 Hz), 5.56 dd (J = 8.1, 15.1 Hz), 5.46 m, 4.36 m, 3.84 q (J = 6.5 Hz), 2.81 dd (J = 7.2, 14.4 Hz), 2.74 dd (J = 6.3, 14.4 Hz), 2.05 s, 1.94 m, 1.82 m, 1.58 m, 1.31 s, 0.91 d (J = 6.4 Hz), 0.90 d (J = 6.4 Hz), 0.89 d (J = 6.3 Hz). 0.88 d (J = 6.3 Hz).

Example 53

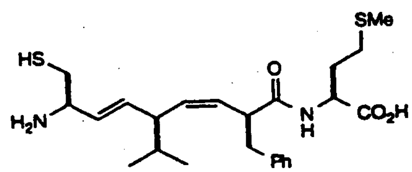
Compound PD301



^1H NMR (CD_3OD) δ: 7.24 m, 7.19 m, 5.75 dd (J = 7.9, 15.4 Hz), 5.62 t (J = 10.4 Hz), 5.41 t (J = 10.6 Hz), 5.30 dd (J = 7.6, 15.6 Hz), 4.29 m, 3.77 q (J = 6.5 Hz), 3.59 q (J = 8.2 Hz), 2.94 m, 2.75 m, 1.5-2.0 m, 0.93 d (J = 6.7 Hz), 0.89 d (J = 6.7 Hz).

Example 54

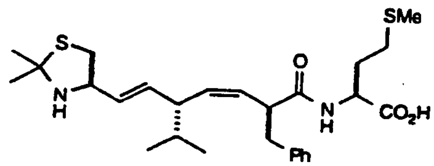
Compund PD311



^1H NMR (CD_3OD) δ: 8.22 d (J = 9.9 Hz), 7.24 m, 7.18 m, 5.70 dd (J = 7.2, 16.6 Hz), 5.67 t (J = 11.1 Hz), 5.36 t (J = 11.1 Hz), 5.08 dd (J = 8.1, 17.0 Hz), 4.48 m, 3.71 q (J = 6.8 Hz), 3.56 q (J = 6.8 Hz), 3.05 dd (J = 6.8, 13.4 Hz), 2.83 q (J = 7.8 Hz), 2.7 m, 2.47 m, 2.38 m, 2.07 m, 2.03 s, 1.90 m, 1.64 oct (J = 4.4 Hz), 0.90 d (J = 6.6 Hz), 0.86 (J = 6.7 Hz).

Example 55

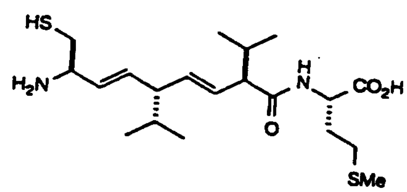
Compound PD321



^{1}H NMR (CD_3OD) δ: 8.11 d (J = 8.2 Hz), 7.26 m, 7.19 m, 5.99 dd (J = 7.9, 15.3 Hz), 5.67 t (J = 10.4 Hz), 5.49 dd (J = 8.6, 15.6 Hz), 5.42 t (J = 10.6 Hz), 4.64 q (J = 8.4 Hz), 4.45 dd (J = 4.2, 9.3 Hz), 3.58 dt (J = 6.6, 9.4 Hz), 3.39 dd (J = 6.9, 11.6 Hz), 3.13 dd (J = 9.9, 11.6 Hz), 2.96 m, 2.69 dd (J = 6.2, 13.4 Hz), 2.5 m, 1.99 s, 1.95 m, 1.80 s, 1.79 s, 1.73 m, 1.66 oct (J = 6.9 Hz), 0.94 d (J = 6.7 Hz), 0.90 d (J = 6.7 Hz).

Example 56

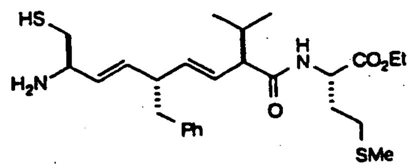
Compound PD341



^{1}H NMR (CD_3OD) δ: 8.23 d (J = 7.7 Hz), 5.89 dd (J = 8.0, 15.4 Hz), 5.54 dd (J = 7.5, 15.2 Hz), 5.45 dd (J = 8.4, 15.9 Hz), 5.41 dd (J = 8.0, 15.7 Hz), 4.52 m, 3.84 q (J = 6.7 Hz), 2.82 dd (J = 6.4, 13.9 Hz), 2.75 dd (J = 6.1, 14.0 Hz), 2.59 m, 2.53 m, 2.47 m, 2.12 m, 2.07 s, 1.94 m, 1.71 m, 1.48 m, 0.95 d (J = 6.6 Hz), 0.93 d (J = 6.4 Hz), 0.91 d (J = 6.6 Hz), 0.89 d (J = 6.9 Hz).

Example 57

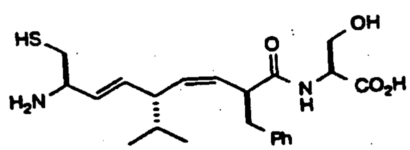
Compound PD351



^1H NMR (CD_3OD) δ: 8.36 d (J = 7.6 Hz), 7.25 m, 7.16 m, 5.89 dd (J = 7.4, 15.7 Hz), 5.55 dd (J = 6.8, 15.5 Hz), 5.45 dd (J = 9.0, 15.5 Hz), 5.40 dd (J = 7.4, 15.5 Hz), 4.48 m, 4.16 q (J = 7.1 Hz), 3.81 q (J = 6.9 Hz), 3.17 pent. (J = 7.1 Hz), 2.77 d (J = 7.3 Hz), 2.75 dd (J = 6.8, 15.0 Hz), 2.68 dd (J = 6.0, 14.0 Hz), 2.53 m, 2.45 m, 2.06 s, 1.89 m, 1.25 t (J = 7.1 Hz), 0.92 (J = 6.6 Hz), 0.83 d (J = 6.7 Hz).

Example 58

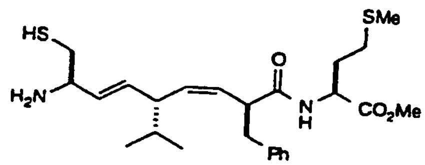
Compound PD361



^1H NMR (CD_3OD) δ: 7.96 d (J = 7 Hz), 7.25 m, 7.20 m, 5.67 dd (J = 8.3, 15.9 Hz), 5.61 t (J = 10.6 Hz), 5.40 t (J = 10.6 Hz), 5.19 dd (J = 7.5, 15.5 Hz), 4.43 m, 3.5-3.8 m, 3.03 m, 2.85 q (J = 8.1 Hz), 2.72 m, 1.6 m, 0.91 d (J = 6.7 Hz), 0.88 d (J = 6.8 Hz).

Example 59

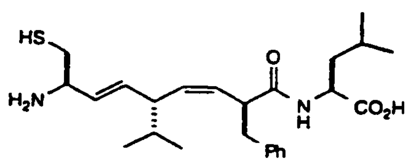
Compound PD371



^1H NMR (CD_3OD) δ: 8.21 d (J = 8.1 Hz), 7.26 m, 7.18 m, 5.82 dd (J = 7.7, 15.4 Hz), 5.65 t (J = 10.4 Hz), 5.40 dd (J = 8.1 15.6 Hz), 5.39 t (J = 10.5 Hz), 4.47 dt (J = 3.3, 6.6 Hz), 4.00 q (J = 7.3 Hz), 3.65 s, 3.57 dt (J = 5.7, 9.6 Hz), 3.07 dd (J = 6.3, 14.1 Hz), 2.95 m , 2.70 dd (J = 5.6, 13.3 Hz), 2.05 m, 1.97 s, 1.89 m, 1.69 m, 0.95 d (J = 6.7 Hz), 0.90 (J = 6.8 Hz).

Example 60

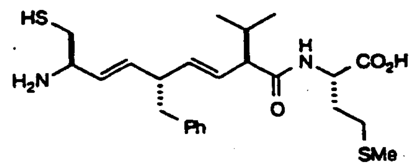
Compound PD381



^1H NMR (CD_3OD) δ: 8.06 d (J = 8.4 Hz), 7.25 m, 7.18 m, 5.78 dd (J = 7.8, 15.5 Hz), 5.64 t (J = 10.2 Hz), 5.41 t (J = 10.5 Hz), 5.34 dd (J = 7.7, 15.3 Hz), 4.34 q (J = 7.4 Hz), 3.79 q (J = 6.4 Hz), 3.59 q (J = 8.3 Hz), 3.30 d (J = 1.5 Hz), 2.94 m, 2.78 dd (J = 6.1, 14.2 Hz), 2.71 dd (J = 5.9, 13.6 Hz), 1.65 m, 1.43 m, 1.12 m, 0.94 d (J = 6.6 Hz), 0.90 d (J = 6.7 Hz), 0.80 d (J = 6.5 Hz), 0.76 d (J = 6.4 Hz).

Example 61

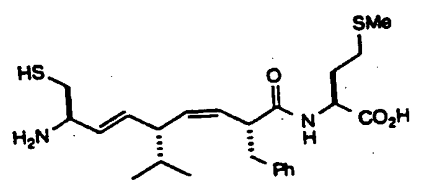
Compound PD391



^1H NMR (CD_3OD) δ: 8.25 d (J = 7.7 Hz), 7.25 m, 7.16 m, 5.89 dd (J = 7.4, 15.7 Hz), 5.56 dd (J = 6.8, 15.5 Hz), 5.46 dd (J = 9.6, 16.2 Hz), 5.40 dd (J = 8.0, 15.6 Hz), 4.48 m, 3.81 q (J = 6.6 Hz), 3.17 pent, (J = 7.1 Hz), 2.77 d (J = 7.4 Hz), 2.75 dd (J = 6.8, 16.0 Hz), 2.68 dd (J = 6.1, 14.2 Hz), 2.54 m, 2.46 m, 2.10 m, 2.07 s, 1.89 m, 0.92 (J = 6.6 Hz), 0.83 d (J = 6.7 Hz).

Example 62

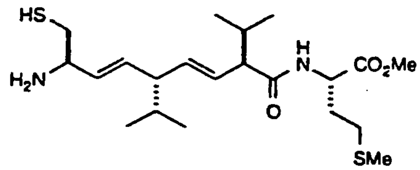
Compound PD401



^1H NMR (CD_3OD) δ: 8.26 d (J = 7.9 Hz), 7.23 m, 7.17 m, 5.81 dd (J = 8.1, 15.6 Hz), 5.48 m, 5.32 dd (J = 7.8, 15.5 Hz), 4.49 m, 3.80 q (J = 6.9 Hz), 3.06 dd (J = 7.2, 13.9 Hz), 2.80 ab m, 2.71 ab m, 2.53 m, 2.46 dd (J = 5.1, 8.1 Hz), 2.39 m, 2.37 m, 2.05 s, 1.89 m, 1.62 oct (J = 6.5 Hz), 0.83 d (J = 6.2 Hz).

Example 63

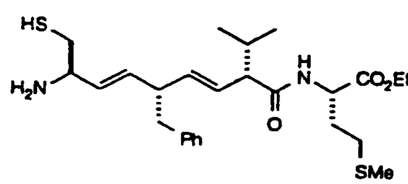
Compound PD411



^1H NMR (CD_3OD) δ: 8.38 d (J = 7.7 Hz), 5.89 dd (J = 8.2, 15.3 Hz), 5.53 dd (J = 7.5, 15.3 Hz), 5.44 dd (J = 9.4, 14.8 Hz), 5.40 ddd (J = 0.8, 8.2, 15.1 Hz), 4.54 ddd (J = 3.1, 6.4, 12.2 Hz), 3.83 q (J = 6.7 Hz), 3.70 s, 2.83 dd (J = 7.6, 13.9 Hz), 2.74 dd (J = 6.0, 14.0 Hz), 2.56 m, 2.45 m, 2.12 m, 2.06 s, 1.93 m, 1.71 oct (J = 6.6 Hz), 0.95 d (J = 6.5 Hz), 0.92 d (J = 6.7 Hz), 0.91 d (J = 6.7 Hz), 0.89 d (J = 6.6 Hz).

Example 64

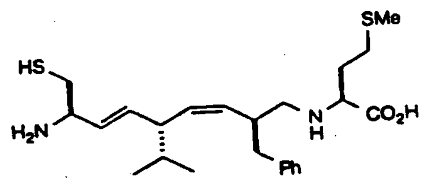
Compound PD421



^1H NMR (CD_3OD) δ: 8.36 d (J = 7.0 Hz), 7.25 m, 7.16 m, 5.93 dd (J = 6.4, 15.7 Hz), 5.4 m, 4.54 m, 4.16 q (J = 7.2 Hz), ~3.8 m 3.17 m, 2.80 m, 2.69 m, 2.54 m, 2.07 s, 0.83 (J = 6.8 Hz), 0.65 d (J = 6.7 Hz).

Example 65

Synthesis of Compound PD431

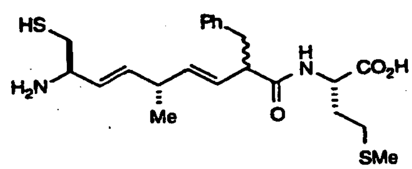


Amine R030D was converted to analog PD431 using the same methods used above for the conversion of ester R024D to analog PD331. The following characteristic values may be obtained by nuclear magnetic resonance spectroscopy:

^{1}H NMR (CD_3OD) δ: 5.60 dd (J = 7.4, 15.5 Hz), 5.54 t (J = 10.0 Hz), 5.36 t (J = 10.2 Hz), 5.14 dd (J = 7.4, 15.4 Hz), 3.79 t (J = 6.1 Hz), 3.11 m, 2.94 m, 2.86 dd (J = 5.4, 13.2 Hz), 2.78 q (J = 8.4 Hz), 2.71 dd (J = 6.0, 14.2 Hz), 2.63 m, 2.14 m (J = 6.6 Hz), 2.09 s, 1.66 oct (J = 7.0 Hz), 0.93 d (J = 6.6 Hz), 0.92 d (J = 6.7 Hz).

Example 66

Compound PD441

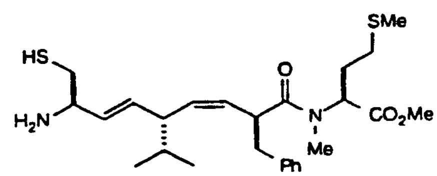


^{1}H NMR (CD_3OD) δ: 8.24 d (J = 8.2 Hz), 8.17 d (J = 8.2 Hz), 7.21 m, 7.15 m, 5.87 dd (J = 6.2, 15.6 Hz), 5.79 dd (J = 6.9, 15.6), 5.55 m, 5.43 dd (J = 6.5, 15.7 Hz), 5.40 dd (J = 7.3, 9.0 Hz), 5.33 dd (J = 7.8, 15.6 Hz), 4.45 m, 3.78 q (J = 6.6 Hz), 3.76 q (J = 6.6 Hz), 3.28 m, 3.04 dd

(J = 7.2, 13.5 Hz), 2.96 dd (J = 10.0, 13.2 Hz), 2.87 m, 2.73 m, 2.46 m, 2.39 m, 2.11 m, 2.03 s, 1.96 s, 1.08 d (J = 6.8 Hz), 1.05 d (J = 6.9 Hz).

Example 67

Synthesis of Compound PD451



Ester **R031D** was converted to analog **PD451** using the same methods used above for the conversion of ester **R025D** to analog **PD331**. The following characteristic values may be obtained by nuclear magnetic resonance spectroscopy:

^1H NMR (CD_3OD) δ: 7.27 m, 7.22 m, 5.84 dd (J = 7.8, 15.6 Hz), 5.62 t (J = 10.4 Hz), 5.47 t (J = 10.1 Hz), 5.42 dd (J = 7.0, 15.0 Hz), 5.03 dd (J = 4.5, 10.3 Hz), 4.07 dt (J = 5.4, 9.4 Hz), 3.83 q (J= 6.9 Hz), 3.63 s, 2.87 s, 2.00 s, 0.97 d (J = 7.3 Hz), 0.93 d (J = 7.4 Hz).

Example 68

Amine R001A

The solid hydrochloride salt of phenylalaninyl methionine methyl ester was added to a solution of aldehyde **R020D** (488 mg, 1.492 mmol) in THF (20 mL). The mixture was stirred at room temp for 15 min until homogeneous. Triacetoxy sodium borohydride (1.392 g, 6.565 mmol) was added and the solution was stirred at room temp for 16 h. The reaction mixture was then diluted with ethyl acetate (100 mL) and water (50 mL) and the two phases were separated. The aqueous phase was extracted twice with ethyl acetate (20 mL). Ethyl acetate extracts were combined and washed with saturated aq sodium bicarbonate and then brine.

The crude product was purified FC (20 g SiO_2) (eluting with 1:3 ethyl acetate:hexanes). Amine **R001A** was obtained as a colorless oil (677 mg, 73%).

^{1}H NMR (CD_3OD) δ: 7.2 - 7.3 m, 5.6 br m, 4.67 m, 5.28 m, 4.67 br m, 4.58 dd (J = 4.6, 8.8 Hz), 3.69 s, 3.36 dd (J = 5.5, 7.9 Hz), 3.23 dd (J = 5.9, 11.8 Hz), 3.04 dd (J = 5.4, 13.7 Hz), 2.81 dd (J = 8.2, 13.6 Hz), 2.69 dd (J = 4.6, 10.9 Hz), 2.34 - 2.45 m, 2.28 m, 2.07 - 2.10 m, 2.05 s, 1.94 m, 1.74 (s x 2, 6H), 1.54 sept (J = 6.8), 1.44 s, 0.85 d (J = 6.8 Hz), 0.82 d (J = 6.9).

Example 69

Acid **R002A**

A solution of lithium hydroxide (95 mg, 3.95 mmol) in water (3 mL) was added to a solution of amine **R001A** (245 mg, 0.395 mmol) in dioxane (3 mL). The resulting cloudy mixture was stirred at room temp for 15 min during which time it became homogeneous. The reaction was quenched by dropwise addition of 0.1 *N* HCl (40 mL) until a pH of 5.7 was obtained. This aqueous solution was extracted four times with chloroform (40 mL). The organic extracts were combined and washed with brine, dried over sodium sulfate and evaporated. The resulting residue was purified by reverse phase HPLC to give acid **R002A** as a white solid (332 mg, >100%).

^{1}H NMR (CD_3OD) δ: 7.27 - 7.37 m, 5.30 br m, 5.37 br m, 4.85 br s, 4.38 dd (J = 4.4, 9.3 Hz), 4.08 t (J= 7.3 Hz), 3.35 dd (J = 6.0, 11.8 Hz), 3.22 d (J = 7.8 Hz), 3.08 dd (J = 4.6, 12.2 Hz), 2.83 br s, 2.66 d (J = 12.0 Hz), 2.41 m, 2.14 - 2.29 m, 2.09 - 2.14 m, 2.04 s, 1.96 m, 1.78 s, 1.76 s, 1.66 br m, 1.49 br s, 0.90 d (J = 6.6 Hz), 0.86 br m.

Example 70

Disulfide R003A

Methoxycarbonylsulfenyl chloride (63 mg, 0.494 mmol) was added to a solution of acid **R002A** (285 mg, 0.395 mmol) in HOAc (10 mL), DMF (1.25 mL) and water (0.625 mL) maintained at 0 °C. The solution was stirred for 4 h, during which time it was allowed to gradually warm to room temp. All volatiles were evaporated under reduced pressure and the residue was purified by reverse phase HPLC to afford disulfide **R003A** (237 mg, 78%) as a white solid.

^1H NMR (CD_3OD) δ: 7.24 - 7.37 m, 5.61 dd (J = 6.4, 15.4 Hz), 5.44 dd (J = 9.8, 15.4 Hz), 4.39 dd (J = 4.4, 9.4 Hz), 4.21 q, (J = 7.0 Hz), 4.09 dd (J = 6.3, 8.4 Hz), 3.92 s, 3.13 - 3.20 m, 2.85 - 3.02 m, 2.41 m, 2.21 - 2.27 m, 2.13 m, 2.04 s, 1.98 m, 1.66 sep (J = 6.6 Hz), 1.45 s, 0.90 d (J = 6.7 Hz), 0.86 d (J = 6.8 Hz).

Example 71

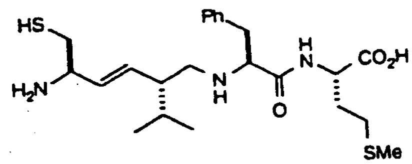
Thiol R004A

Tri-*n*-butyl phosphine (310 mg, 1.535 mmol) was added to a solution of disulfide **R003A** (237 mg, 0.307 mmol) in THF (10 mL) and H_2O (1 mL). The solution was stirred at room temp for 2 h. Volatiles were removed under reduced pressure and the residue was purified by reverse phase HPLC to afford thiol **R004A** as an impure yellow oil (338 mg, >100%, contaminated by tri-*n*-butyl phosphine).

^1H NMR (CD_3OD) δ: 8.67 d (J = 8.6 Hz), 7.27 - 7.36 m, 5.62 dd (J = 6.2, 15.2 Hz), 5.39 dd (J = 9.5, 15.2 Hz), 4.38 br m, 4.06 m , 3.21 d (J = 7.5 Hz), 3.11 dd (J = 4.8, 12.0 Hz), 2.83 t (J = 12.4 Hz), 2.63 - 2.67 br m, 2.41 m, 2.19 - 2.31 m, 2.13 m, 2.04 s, 1.96 m, 1.66 m, 1.46 s, 0.90 d (J = 6.7 Hz), 0.85 d (J = 6.8 Hz).

Example 72

Compound PA041



TFA (5 mL) was added to a solution of crude *N*-BOC-protected thiol **R004A** (338mg, 0.037 mmol) in dichloromethane (0.5 mL) and triethylsilane (0.5 mL) cooled in an ice-water bath. After the addition was complete, the cooling bath was removed and the solution was stirred at room temp for 1 h. All volatiles were removed under reduced pressure and the residue was purified by reverse phase HPLC. After lyophilization, analog **PA041** was obtained as a white powder (109 mg, 51%). ^{1}H NMR (CD_3OD) δ: 7.27 - 7.36 m, 5.73 dd (J = 8.7, 15.5 Hz), 5.67 dd (J = 6.9, 15.4 Hz), 4.36 dd (J = 4.4, 9.4 Hz), 4.13 dd (J = 6.1, 8.6 Hz), 3.89 q (J = 6.6 Hz), 3.23 dd (J = 5.9, 13.6 Hz), 3.19 dd (J = 8.4, 13.4 Hz), 3.13 dd (J = 5.3, 12.4 Hz), 3.00 dd (J = 9.7, 12.3 Hz), 2.89 dd (J = 6.0, 14.0 Hz), 2.83 dd (J = 6.1, 14.5 Hz), 2.37 m, 2.21 m, 2.12 m, 2.03 s, 1.96 m, 1.77 o (J = 5.7 Hz), 0.95 d (J = 6.8 Hz), 0.90 d (J = 6.8 Hz).

Example 73

Disulfide R005A

Methoxycarbonylsulfenyl chloride (77 mg, 0.605 mmol) was added to a solution of amine **R001A** (250 mg, 0.403 mmol) in HOAc (8 mL), DMF (1 mL), and water (0.5 mL) at 0 °C. The solution was stirred for 2 h, during which time it was allowed to gradually warm to room temp. All volatiles were removed under reduced pressure and the residue was purified

by reverse phase HPLC. Disulfide **R005A** was obtained as an oil (244 mg, 77%).

^{1}H NMR (CD_3OD) δ: 7.23 - 7.37 m, 5.61 dd (J = 6.6, 15.7 Hz), 5.44 dd (J = 10.1, 15.7 Hz), 4.47 dd (J = 4.5, 9.0 Hz), 4.21 q (J = 6.7 Hz), 4.08 t (J = 7.2 Hz), 3.92 s, 3.66 s, 3.09 - 3.20 m, 2.82 - 3.02 m, 2.41 m, 2.20 - 2.30 m, 2.09 m, 2.03 s, 1.93 m, 1.67 m, 1.45 s, 0.91 d (J = 6.7 Hz), 0.86 d (J = 6.7 Hz).

Example 74

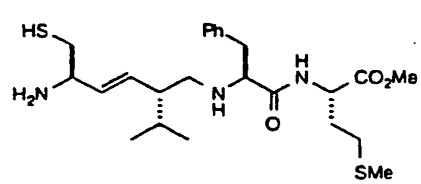
Thiol **R006A**

Tri-*n*-butyl phosphine (251 mg, 1.243 mmol) was added to a solution of disulfide **R005A** (244 mg, 0.311 mmol) in THF (10 mL) and water (1 mL). The solution was stirred at room temp for 2 h. Volatiles were removed under reduced pressure and the residue was purified by reverse phase HPLC to yield thiol **R006A** as an impure colorless oil (235 mg, >100%, contaminated by tri-*n*-butyl phosphine).

^{1}H NMR (CD_3OD) δ: 7.27 - 7.38 m, 5.62 dd (J = 5.6, 15.4 Hz), 5.39 dd (J = 10.2, 15.4 Hz), 4.46 dd (J = 4.5, 9.7 Hz), 4.05 - 4.11 m, 3.67 s, 3.18 - 3.22 m, 3.07 dd (J = 4.7, 12.5 Hz), 2.83 t (J = 11.4 Hz), 2.65 d (J = 6.8 Hz), 2.40 m, 2.20 - 2.30 m, 2.08 m, 2.03 s, 1.93 m, 1.67 m, 1.47 s, 0.90 d (J = 6.7 Hz), 0.86 d (J = 6.8 Hz).

Example 75

Compound **PA091**

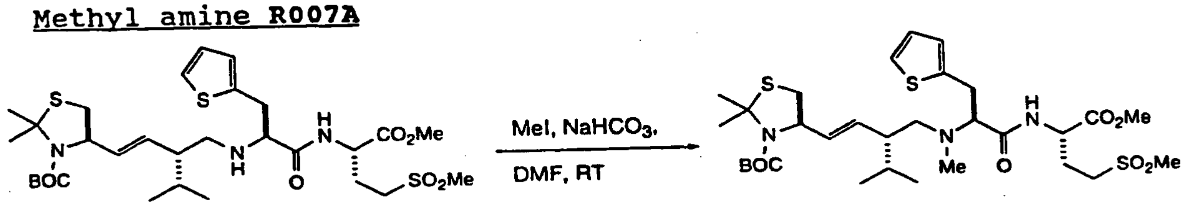


TFA (10 mL) was added to a solution of crude BOC-protected **R006A** (235 mg, 0.311 mmol) in dichloromethane (1 mL) and triethylsilane (1 mL) cooled in an ice-water bath. After the addition was complete, the cooling bath was removed and the solution was stirred at room temp for an additional 3 h. All volatiles were removed under reduced pressure and the residue was purified by reverse phase HPLC. After lyophilization, compound **PA091** was obtained as a white powder (115 mg, 52%).

^1H NMR (CD_3OD) δ: 7.26 - 7.37 m, 5.74 dd (J = 8.7, 15.5 Hz), 5.67 dd (J = 6.8, 15.5 Hz), 4.44 dd (J = 4.6, 9.3 Hz), 4.13 dd (J = 5.6, 9.2 Hz), 3.90 q (J = 6.3 Hz), 3.66 s, 3.24 dd (J = 5.6, 13.4 Hz), 3.16 dd (J = 9.3, 13.4 Hz), 3.09 dd (J = 5.5, 12.3 Hz), 3.01 dd (J = 9.5, 12.2 Hz), 2.89 dd (J = 5.9, 14.3 Hz), 2.83 dd (J = 6.2, 14.3 Hz), 2.37 m, 2.24 m, 2.04-2.12 m, 2.03 s, 1.93 m, 1.78 o (J = 5.6 Hz), 0.96 d (J = 6.7 Hz), 0.91 d (J = 6.8 Hz).

Example 76

Methyl amine **R007A**



R008A R007A

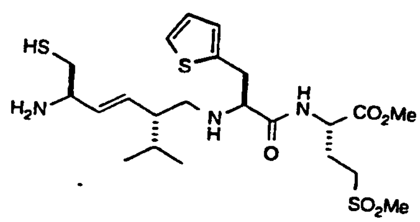
Methyl iodide (54 mg, 0.377 mmol) was added to a solution of amine **R008A** (226 mg, 0.343 mmol) in DMF (5 mL). The resulting mixture was stirred for 1 h at room temp. Sodium bicarbonate (32 mg, 0.377 mmol) was added and the resulting suspension was stirred at room temp for 24 h. Two percent aqueous sodium bicarbonate solution (50 mL) was added and the mixture was extracted four times with ethyl

acetate (20 ml). The acetate extracts were combined, washed by brine, and dried over sodium sulfate. The volatiles were removed under reduced pressure and a yellowish oil residue was obtained. It was purified by FC (eluting with 1:1 ethyl acetate:hexanes). The desired methyl amine **R007A** (109 mg, 47%) was obtained as a colorless oil.

^{1}H NMR (CD_3OD) δ: 7.19 dd (J = 0.7, 4.9 Hz), 6.87 - 6.91 m, 5.30 - 5.72 br m, 4.84 br m, 4.47 br m, 3.71 s, 3.52 br m, 3.27 - 3.36 m, 2.90 - 3.12 br m, 3.09 dd (J = 5.8, 14.8 Hz), 2.94 s, 2.64 dd (J = 5.4, 12.4 Hz), 2.57 d (J = 11.8 Hz), 2.21 - 2.38 br m, 2.30 s, 2.11 m, 1.76 s, 1.75 s, 1.46 s, 0.87 d (J = 5.9 Hz), 0.83 d (J = 6.5 Hz).

Example 77

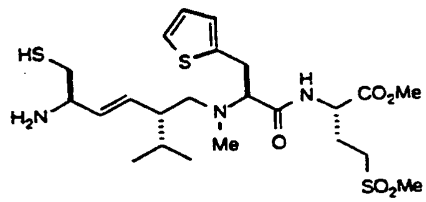
Compound **PA011**



^{1}H NMR (CD_3OD): δ: 7.36 dd (J = 1.2, 4.9 Hz), 6.99 - 7.02 m, 5.75 dd (J = 9.2, 15.5 Hz), 5.65 dd (J = 7.4, 15.6 Hz), 4.48 dd (J = 5.0, 8.8 Hz), 4.11 br t (J = 6.8 Hz), 3.89 dd (J = 6.1, 13.3 Hz), 3.73 s, 3.44 d (J = 7.1 Hz), 3.15 dd (J = 5.6, 12.4 Hz), 2.91 - 3.05 m, 2.95 s, 2.87 dd (J = 6.0, 14.3 Hz), 2.82 dd (J = 6.2, 14.3 Hz), 2.33 - 2.43 m, 2.22 m, 1.79 m, 0.97 d (J = 6.8 Hz), 0.92 d (J = 6.8).

Example 78

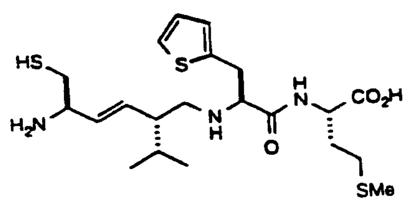
Compound PA021



^1H NMR (CD_3OD) δ: 7.34 dd (J = 2.1, 4.1 Hz), 6.99 - 7.01 m, 5.81 dd (J = 9.4, 15.6 Hz), 5.67 br m, 4.43 dd (J = 5.1, 8.7 Hz), 4.07 br m, 3.89 dd (J = 6.4, 13.4 Hz), 3.71 s, 3.51 br m, 3.12 - 3.30 br m, 2.77 - 3.02 br m, 2.95 s, 2.49 br, 2.37 m, 2.21 m, 1.81 m, 0.97 d (J = 6.8 Hz), 0.92 d (J = 6.8 Hz).

Example 79

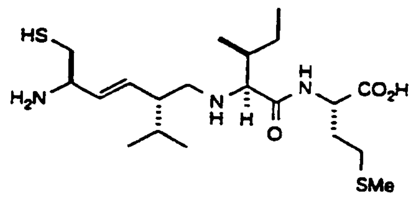
Compound PA031



^1H NMR (CD_3OD) δ: 7.30 dd (J = 1.7, 4.0 Hz), 6.96 m, 5.71 dd (J = 9.5, 15.4 Hz), 5.60 dd (J = 7.6, 15.8 Hz), 4.44 dd (J = 4.4, 9.1 Hz), 3.98 bm, 3.86 q (J = 6.5 Hz), 3.45 dd (J = 7.4, 14.7 Hz), 3.38 dd (J = 6.4, 14.8 Hz), 3.07 dd (J = 4.9, 11.9 Hz), 2.92 bt (J = 10.7 Hz), 2.85 dd (J = 5.9, 13.9 Hz), 2.80 dd (J = 5.9, 13.9 Hz), 2.47 ddd (J = 5.1, 8.0, 13.1 Hz), 2.34 m, 2.16 m, 2.07 s, 2.02 m, 1.76 o (J = 6.4 Hz), 0.96 d (J = 6.7 Hz), 0.92 d (J = 6.8 Hz).

Example 80

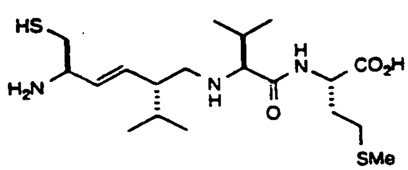
Compound PA051



^1H NMR (CD_3OD) δ: 5.75 dd (J = 9.2, 15.5 Hz), 5.65 dd (J = 7.5, 15.6 Hz), 4.65 dd (J = 4.4, 9.8 Hz), 3.89 q (J = 6.6 Hz), 3.76 d (J = 4.8 Hz), 3.08 dd (J = 5.9, 12.4 Hz), 3.03 dd (J = 8.5, 12.5 Hz), 2.87 d (J = 6.2 Hz), 2.64 ddd (J = 5.2, 7.9, 13.1 Hz), 2.54 dt (J = 13.5, 7.8 Hz), 2.39 m, 2.24 m, 2.10 s, 2.03 s, 1.81 o (J = 6.2 Hz), 1.66 m, 1.39 m, 1.03 d (J = 6.9 Hz), 0.99 d (J= 7.5 Hz), 0.97 d (J = 6.9 Hz), 0.91 d (J = 6.8 Hz).

Example 81

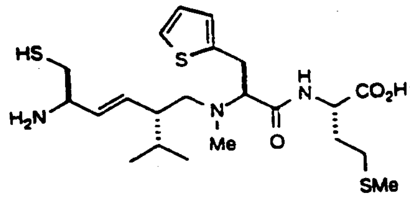
Compound PA061



^1H NMR (CD_3OD) δ: 5.73 dd (J = 9.2, 15.6 Hz), 5.64 (dd J= 7.9, 16.0 Hz), 4.65 dd (J = 4.2, 9.8 Hz), 3.89 q (J = 6.5 Hz), 3.73 d (J = 5.4 Hz), 3.07 m, 2.87 d (J = 6.1 Hz), 2.65 ddd (J = 5.1, 7.6, 12. 7 Hz), 2.56 dt (J = 13.3, 7.7 Hz), 2.40 m, 2.28 m, 2.11 s, 2.05 m, 1.82 o (J = 6.2 Hz), 1.18 d (J = 6.9 Hz), 1.07 d (J = 6.8 Hz), 0.99 (J = 6.7 Hz), 0.93 d (J = 6.8 Hz).

Example 82

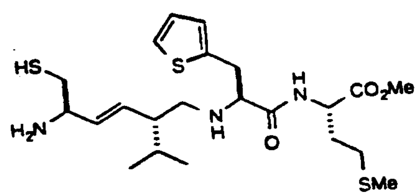
Compound PA071



^1H NMR (CD_3OD) δ: 7.31 m, 6.96 - 7.00 m, 5.80 dd (J = 9.4, 15.5 Hz), 5.65 dd (J = 7.6, 15.4 Hz), 4.40 dd (J=4.5, 9.1 Hz), 4.06 br m, 3.88 dd (J = 6.4, 13.5 Hz), 3.45 - 3.57 m, 3.10 - 3.27 m, 2.72 - 2.89 m, 2.79 br s, 2.41 - 2.47 m, 2.33 m, 2.13 m, 2.05 s, 2.00 m, 1.77 m, 0.95 d (J = 6.8 Hz), 0.91 d (J = 6.8 Hz).

Example 83

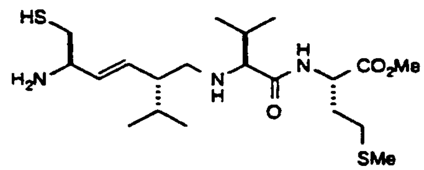
Compound PA081



^1H NMR (CD_3OD) δ: 7.31 dd (J = 2.6, 3.7 Hz), 6.97 m, 5.71 dd (J = 9.2, 15.4 Hz), 5.63 dd (J = 7.3, 15.4 Hz), 4.51 dd (J = 4.6, 9.2 Hz), 4.06 bm, 3.87 q (J = 6.4 Hz), 3.70 s, 3.43 m, 3.09 dd (J = 5.1, 11.9 Hz), 2.98 bt (J = 10.9 Hz), 2.87 dd (J = 6.2, 14.3 Hz), 2.81 dd (J = 6.6, 14.7 Hz), 2.47 ddd (J = 5.4, 7.7, 13.1 Hz), 2.35 m, 2.13 m, 2.06 s, 2.00 m, 1.78 o (J = 6.3 Hz), 0.99 d (J = 7.5 Hz), 0.93 d (J = 6.8 Hz).

Example 84

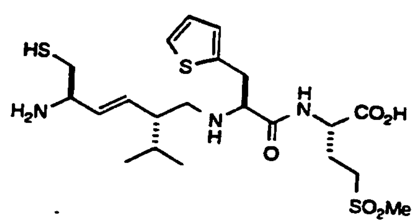
Compound PA101



^1H NMR (CD_3OD) δ: 5.73 dd (J = 9.2, 15.5 Hz), 5.63 dd (J = 8.0, 15.5 Hz), 4.70 dd (J = 4.4, 9.7 Hz), 3.89 q (J = 6.5 Hz), 3.73 s, 3.73 d (J - 4 Hz), 3.05 m, 2.87 d (J = 6.1 Hz), 2.64 ddd (J = 5.3, 7.6, 12.9 Hz), 2.55 dt (J = 14.4, 7.2 Hz), 2.40 m, 2.25 m, 2.10 s, 2.04 m, 1.82 o (J = 6.2 Hz), 1.17 d (J = 6.9 Hz), 1.07 d (J = 6.8 Hz), 0.99 d (J = 6.7 Hz), 0.93 d (J = 6.8 Hz).

Example 85

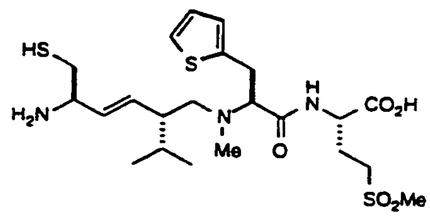
Compound PA111



^1H NMR (CD_3OD): δ: 7.34 dd (J = 2.3, 4.0 Hz), 6.97 - 7.01 m, 5.74 dd (J = 9.3, 15.5 Hz), 5.65 dd (J = 7.5, 15.6 Hz), 4.39 dd (J = 4.9, 8.4 Hz), 4.08 br t (J = 7.0 Hz), 3.88 dd (J = 6.2, 13.3 Hz), 3.41 - 3.49 m, 3.16 dd (J = 5.4, 12.3 Hz), 2.95 - 3.11 m, 2.95 s, 2.87 dd (J = 5.9, 14.3 Hz), 2.81 dd (J = 6.2, 14.3 Hz), 2.45 - 2.19 m, 1.78 m, 0.96 d (J = 6.7 Hz), 0.91 d (J = 6.8 Hz).

Example 86

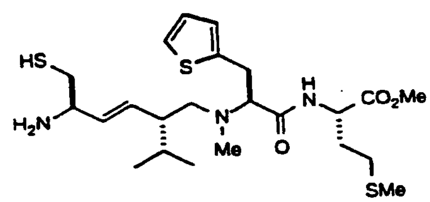
Compound PA121



^1H NMR (CD_3OD) δ: 7.32 dd (J = 1.6, 4.6 Hz), 6.97 - 7.01 m, 5.80 dd (J = 9.4, 15.6 Hz), 5.65 dd (J = 7.7, 15.6 Hz), 4.35 dd (J = 5.0, 8.5 Hz), 4.05 br m, 3.88 dd (J = 6.3, 13.4 Hz), 3.46 - 3.56 m, 3.11 - 3.30 br m, 2.78 - 3.03 m, 2.95 s, 2.35 - 2.48 m, 2.23 m, 1.78 m, 0.96 d (J = 6.7 Hz), 0.91 d (J = 6.8 Hz).

Example 87

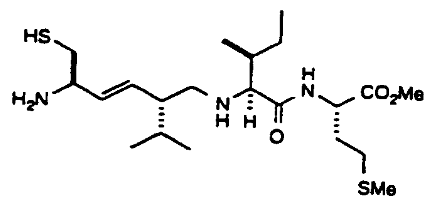
Compound PA131



^1H NMR (CD_3OD) δ: 7.34 dd (J = 1.4, 4.9 Hz), 6.97 - 7.00 m, 5.81 dd (J = 9.4, 15.6 Hz), 5.70 dd (J = 7.3, 15.8 Hz), 4.45 dd (J = 4.7, 9.3 Hz), 4.16 br m, 3.89 dd (J = 6.3, 13.4 Hz), 3.69 s, 3.54 br d (J = 6.5 Hz), 3.29 br, 2.88 br s, 2.80 - 2.89 m, 2.51 br, 2.42 m, 2.28 m, 2.10 m, 2.04 s, 1.97 m, 1.78 m, 0.97 d (J = 6.8 Hz), 0.92 d (J = 6.8 Hz).

Example 88

Compound PA141



^{1}H NMR (CD_3OD) δ: 5.75 dd (J = 9.2, 15.6 Hz), 5.66 dd (J = 7.4, 15.5 Hz), 4.71 dd (J = 4.4, 9.8 Hz), 3.89 q (J = 6.5 Hz), 3.80 d (J = 4.7 Hz), 3.73 s, 3.06 d (J = 7.2 Hz), 2.88 dd (J = 6.1, 14.2 Hz), 2.84 dd (J = 6.2, 14.1 Hz), 2.63 ddd (J = 5.4, 7.6, 13.0 Hz), 2.54 dt (J = 13.6, 7.6 Hz), 2.41 m, 2.20 m, 2.09 s, 2.02 m, 1.81 o (J = 6.3 Hz), 1.66 m, 1.36 m, 1.02 d (J = 6.9 Hz), 0.99 d (J = 7.0 Hz), 0.96 d (J = 6.6 Hz), 0.91 d (J = 6.8 Hz).

Example 89

Bromoolefins R002E

Sodium hydride (250 mg, 10.4 mmol) was added to a solution of L-(-)-methyl α-hydroxy-β-phenyl propionate (3.6 g, 20 mmol) and 1,3-dibromo propene (8.24 g, 41 mmol) in CH_3CN (60 mL) under argon at ambient temperature. Additional quantities of sodium hydride (650 mg, 27 mmol) were added batchwise at 2, 6, and 20 h. TLC (1:4 ethyl acetate:hexanes) showed complete consumption of starting material 5 h after the final sodium hydride addition. The resulting brown mixture was quenched with brine and extracted with ethyl acetate. The extract was dried with brine, dried with $MgSO_4$ and evaporated to give 5.7 g of crude product. Purification by FC (eluting with 1:9 ethyl acetate:hexanes) afforded the desired bromoolefins R002E

(3.68 g, 62%) as a mixture of *cis:trans* olefins in a ratio of approximately 1:1. Separation of the olefin isomers could be achieved by more exhaustive chromatography. A small amount of alkyne derived from elimination of the desired bromoolefinic products was also isolated (136 mg, 3%).

^{1}H NMR ($CDCl_3$) δ *cis* isomer: 7.31 - 7.22 m , 6.24 m, 6.13 m, 4.23 m, 4.13 ~ 4.09 m , 3.74 s, 3.1 ~ 2.9 m.

^{1}H NMR ($CDCl_3$) δ *trans* isomer: 7.33 ~ 7.21 m, 6.20 ~ 6.10 m, 4.1 ~ 4.0 m, 3.80 dd (J = 5.6, 13.2 Hz), 3.73 s, 3.09 ~ 2.95 m.

^{1}H NMR ($CDCl_3$) δ alkyne: 7.31 - 7.21 m, 4.38 dd (J = 5.1, 7.6 Hz), 4.26 dd (J = 2.4, 16.1 Hz), 4.15 dd (J = 2.4, 16.1 Hz), 3.72 s, 3.1 - 3.0 m, 2.39 t (J = 2.4 Hz).

Example 90

<u>Alcohols R003E</u>

A mixture of bromoolefins **R002E** slightly enriched in the *trans* isomer (*cis:trans* ratio = 2:3) (2.533 g, 4.7 mmol), aldehyde **R015D** (3.9 g, 15.9 mmol) and a stirring bar in a 250 mL flask were dried on a vacuum line for 2 h at room temp and then placed under an argon atmosphere. DMSO (130 mL), freshly distilled from CaH_2, was added by cannula under argon pressure. The mixture was placed in a dry box, then $CrCl_2$ (9 g, 73 mmol) and $Ni(COD)_2$ (90 mg, 0.32 mmol) were added with stirring. The resulting mixture was stirred for an additional 3 d, then quenched with ammonium chloride solution and extracted with ethyl acetate (6 x 150 mL). The extract was washed with ammonium chloride solution, dried with $MgSO_4$ and evaporated to give 5.95 g of crude product. Purification by FC (eluting with 1:3 ethyl acetate:hexanes)

furnished the desired alcohols **R003E** (2.51 g, 64%) as a 1:2.3 mixture of diastereomers.

Both diastereomers appear to contain a *trans* olefin. Moreover, similar mixtures of *trans* products are obtained irrespective of the configuration(s) of the starting bromoolefins.

^1H NMR ($CDCl_3$) δ: 7.3 ~ 7.2 m, 5.7 ~ 5.6 m, 4.45 br m, 4.34 br m, 4.15 ~ 4.0 m, 3.85 m, 3.72 s and 3.71 s (ratio 1:2.3), 3.07 ~ 2.99 m, 2.86 m, 1.78 s and 1.76 s, 1.50 s and 1.46 s.

Example 91

Trifluoroacetates **R004E**

Trifluoroacetic acid anhydride (5.56 g, 26.5 mmol) and triethylamine (3.96 g, 39.2 mmol) were added at room temp to a solution of alcohol **R003E** (2.40 g, 5.16 mmol) stirring in CH_2Cl_2 (80 mL). The mixture was stirred for 3 ~ 4 h and then quenched with brine, evaporated to remove CH_2Cl_2, and partitioned between ethyl acetate and water. The organic layer was separated and dried with $MgSO_4$, filtered, and evaporated to afford the crude product (5.6 g). Purification by FC (eluting with 1:3 ethyl acetate:hexanes) furnished trifluoroacetates **R004E** (2.53 g, 87%) as a mixture of alcohol diastereomers.

^1H NMR ($CDCl_3$) δ: 7.3 ~ 7.2 m, 5.83 m, 5.72 m, 5.65 m, 4.55 br m, 4.2 ~ 4.0 m, 3.85 br m , 3.73 s and 3.70 s (in the ratio of 1 / 2.3), 3.11 ~ 2.95 m, 2.75 m, 1.76 ~ 1.63 m , 1.47 s and 1.45 s .

Example 92

Ester **R005E**

Cuprous cyanide (1.84 g, 20.5 mmol) and a stirring bar were heated with a heat gun under vacuum for 10 min. Freshly distilled THF (150 mL) was added by syringe and the

resulting suspension was cooled to -60 °C. A 2 M solution of *i*-PrMgCl in ether (18 mL, 36 mmol) was injected and the mixture was stirred for 10 min. The dry ice bath was then replaced with an ice/water bath. Stirring was continued for an additional 1.5 h at which time the reaction mixture had become very dark.

The mixture prepared above was cooled to -78 °C and trifluoroacetates **R004E** (2.26 g, 4.03 mmol) dissolved in freshly distilled THF (20 mL) were added dropwise over 6 min. 20 min later the reaction mixture was quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate. After drying the organic extracts with $MgSO_4$, filtration, and evaporation of solvent, a crude product was obtained (2.1 g). Purification by FC (eluting with 8% ethyl acetate:hexanes) gave the desired esters **R005E** (1.638 g, 50%) as a mixture of diastereomers in a ratio of 93:7 as determined by HPLC.

^{1}H NMR ($CDCl_3$) δ: 7.27 - 7.20 m, 5.6 dd (J = 7.3, 15.1 Hz), 5.42 m, 4.75 br s, 4.0 dd (J = 4.8, 8.2 Hz), 3.71 s, 3.58 dd (J = 6.2, 9.0 Hz), 3.25 - 3.15 m), 3.0 - 2.9 m, 2.51 m, 2.05 m, 1.77 s, 1.70 m, 1.45 s, 0.79 d (J = 7.2 Hz), 0.77 d (J = 6.9 Hz).

Example 93

Acid R006E

A 0.78 M solution of LiOH (19 mL, 14.4 m mol) was added to a solution of methyl ester R005E (694 mg, 1.41 mmol) stirring in dioxane (20 mL) at room temp. The mixture was stirred overnight until TLC confirmed the disappearance of starting material. The solution was acidified with 0.5 *N* HCl and extracted with ethyl acetate. The organic layer was dried with $MgSO_4$, filtered, and concentrated to a crude product. The desired acid R006E (646 mg, 96%) was obtained

after purification by FC (eluting with 1:4 methanol:ethyl acetate).

^{1}H NMR ($CDCl_3$) δ: 7.25 ~ 7.15 m , 5.55 m, 5.33 dd (J = 9.1, 15.0 Hz), 4.65 br m, 3.92 m, 3.66 m, 3.21 m, 3.19 ~ 3.03 m, 2.84 m, 2.40 m, 1.97 m, 1.72 s, 1.71 s, 1.51 m, 1.41 s, 0.74 d (J = 6.6 Hz), 0.71 d (J = 6.7 Hz).

Example 94

Tert-butyl ester **R007E**

Acid **R006E** (66 mg, 0.14 mmol), *tert*-butyl methionine hydrochloride (40.6 mg, 0.17 mmol), EDC (45 mg, 0.23 mmol), HOBT (21.7 mg, 0.16 mmol) and a stirring bar were placed in a flask and dried under vacuum for 15 min, then DMF (4.5 mL) and *N*-methyl morpholine (19.2 mg, 0.19 mmol) were added by syringe. The resulting mixture was stirred for 18 h then partitioned between ethyl acetate and brine. The organic layer was washed successively with brine, pH 2 phosphate buffer, and then water. The organic extracts were dried with $MgSO_4$, filtered, and concentrated to afford a light yellow oil (110 mg). Purification by FC (eluting with 3:7 ethyl acetate: hexanes) afforded the desired *tert*-butyl ester **R007E** quantitatively.

^{1}H NMR ($CDCl_3$) δ: 7.23 ~ 7.13 m, 6.95 d (J = 7.8 Hz), 5.65 dd (J = 7.1, 14.7 Hz), 5.45 br m, 4.78 br m, 4.48 m , 3.93 dd (J = 3.4, 6.3 Hz), 3.54 dd (J = 5.4, 8.6 Hz), 3.34 dd (J = 6.9, 8.9 Hz), 3.22 dd (J = 5.9, 11.4 Hz), 3.10 dd (J = 3.4, 13.9 Hz), 2.89 dd (J = 6.7, 13.9 Hz), 2.55 d (J = 11.5 Hz), 2.03 s, 1.9 ~ 1.6 m, 1.85 ~ 1.50 m, 1.75 s , 1.45 s and 1.43 s, 0.86 ~ 0.71 m.

Example 95

<u>Disulfide **R008E**</u>

Methoxycarbonyl sulfenyl chloride (11.7 mg, 0.093 mmol) was added to a solution of *tert*-butyl ester **R007E** (47.2 mg, 0.071 mmol) in 20:2:1 HOAc:DMF:H_2O (1.2 mL) at 0 °C. The mixture was warmed to room temp and then stirred for 1 h. After removal of all solvents under vacuum, the crude residue was purified by preparative reverse phase HPLC to afford the desired disulfide **R008E** (41.5 mg, 81%).

^1H NMR ($CDCl_3$) δ: 7.3 ~ 7.2 m, 7.06 d (J = 7.8 Hz), 5.58 ~5.41 m, 5.18 br m, 4.54 m, 4.51 br m, 3.99 dd (J = 3.5, 7.0 Hz), 3.89 s, 3.54 dd (J = 5.0, 9.2 Hz), 3.40 m, 3.14 dd (J = 3.4, 14.1 Hz), 3.01 br m, 2.91 dd (J = 7.1, 14.1 Hz), 2.20 ~ 1.90 m, 2.04 s , 1.90 ~ 1.65 m, 1.46 s, 0.82 d (J = 6.8 Hz), 0.79 d (J = 6.7 Hz).

Example 96

<u>Thiol **R009E**</u>

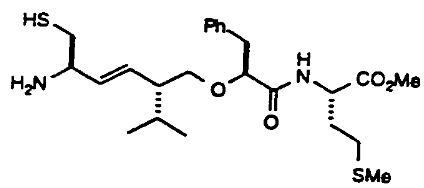
Tri-*n*-butylphosphine (81.2 mg, 0.040 mmol) was added to a solution of disulfide **R008E** (33 mg, 0.046 mmol) dissolved in THF (0.8 mL) and water (27 mg, 1.48 mmol). After stirring for 2 h at room temp, the mixture was evaporated to dryness, dissolved in CH_3CN (2.5 mL) and purified by preparative reverse phase HPLC to afford the desired thiol **R009E** (25.7 mg, 89%).

^1H NMR ($CDCl_3$) δ: 7.34 ~ 7.14 m, 6.99 d (J = 8.3 Hz), 5.47 dd (J = 8.6, 15.4 Hz), 5.34 dd (J = 5.5, 15.4 Hz), 4.93 d (J = 8.6 Hz), 4.51 m , 4.31 br m, 3.95 dd (J = 3.5, 6.7 Hz), 3.52 dd (J = 4.9, 9.2 Hz), 3.38 m , 3.12 dd (J = 3.4, 13.9 Hz), 2.89 dd (J = 6.8, 14.0 Hz), 2.69 ~ 2.67 m, 2.20 ~ 1.90 m, 2.12 s, 1.81 m, 1.66 m, 1.45 br s, 0.82 d

(J = 6.9 Hz), 0.80 d (J = 8.5 Hz).

Example 97

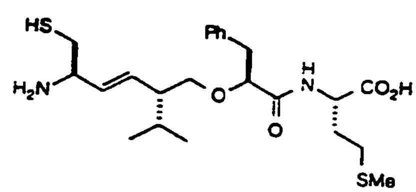
Compound PE011



^{1}H NMR (CD_3OD) δ: 7.98 d (J = 8.1 Hz), 7.18 - 7.28 m, 5.84 dd (J = 9.5, 15.9 Hz), 5.47 dd (J = 7.9, 15.5 Hz), 4.61 m, 4.02 dd (J = 4.4, 7.0 Hz), 3.82 q (J = 6.7 Hz), 3.72 s, 3.61 dd (J = 4.7, 9.3 Hz), 3.45 dd (J = 6.9, 9.2 Hz), 3.06 dd (J = 4.2, 14.0 Hz), 2.79 dd (J = 6.0, 14.1 Hz), 2.70 dd (J = 6.3, 14.1 Hz), 2.26 m, 2.14 m, 2.03 s, 1.91 m, 1.73 o (J = 6.7 Hz), 0.87 d (J = 6.9 Hz), 0.84 d (J = 6.7 Hz).

Example 98

Compound PE021

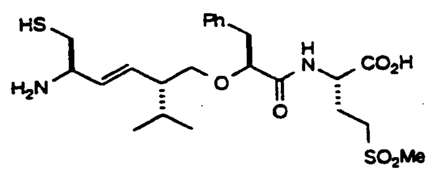


Thiol **R009E** (13 mg, 0.0208 mmol) was dried under vacuum, then TFA (0.76 mL) and Et_3SiH (0.24 mL) were added at 0°C under argon. The mixture was stirred for 3 h, then evaporated to dryness, dissolved in of CH_3CN (2 mL)and purified by preparative reverse phase HPLC to furnish pure analog **PE021** (10.6 mg, 84%).

^1H NMR (CD_3OD) δ: 7.85 d (J = 8.1 Hz), 7.15 - 7.28 m, 5.85 dd (J = 9.1, 15.4 Hz), 5.47 dd (J = 7.7, 15.5 Hz), 4.56 dd (J = 4.6, 8.2 Hz), 4.02 dd (J = 4.1, 7.1 Hz), 3.81 q (J = 3.81 Hz), 3.61 dd (J = 4.6, 9.3 Hz), 3.47 dd (J = 6.8, 9.3 Hz), 3.08 dd (J = 4.0, 14.0 Hz), 2.92 dd (J = 7.2, 14.1 Hz), 2.78 dd (J = 6.0, 14.2 Hz), 2.69 dd (J = 6.4, 14.2 Hz), 2.27 m, 2.03 s, 1.90 m, 1.73 o (J = 6.8 Hz), 0.87 d (J = 6.8 Hz), 0.84 d (J = 6.7 Hz).

Example 99

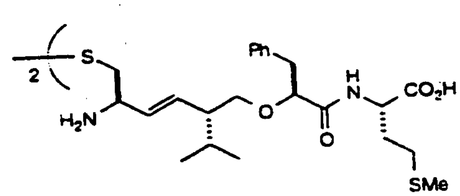
<u>Compound PE031</u>



^1H NMR (CD_3OD) δ: 7.95 d (J = 8.0 Hz), 7.20 - 7.30 m, 5.85 dd (J = 9.2, 15.6 Hz), 5.47 dd (J = 7.8, 15.4 Hz), 4.56 m, 4.04 dd (J = 4.2, 7.0 Hz), 3.82 q (J = 6.6 Hz), 3.63 dd (J = 4.7, 9.3 Hz), 3.47 dd (J = 7.0, 9.3 Hz), 3.09 dd (J = 4.1, 14.1 Hz), 2.96 m, 2.93 s, 2.76 - 2.84 m, 2.70 dd (J = 6.3, 14.1 Hz), 2.32 m, 2.11 m, 1.73 o (J = 5.8 Hz), 0.87 d (J = 6.9 Hz), 0.84 d (J = 6.7 Hz).

Example 100

<u>Compound PE041</u>



A small sample of **PE201** (3.0 mg, 0.0051 mmol) in CD_3OD was left on the bench at room temp and oxidized by ambient

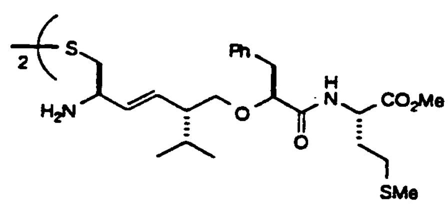
oxygen. The solution was evaporated and purified by preparative reverse phase HPLC to afford analog **PE041** (1.18 mg, 40%).

^{1}H NMR (CD_3OD) δ: 7.18 - 7.28 m, 5.94 dd (J = 9.1, 15.5 Hz), 5.53 dd (J = 7.6, 15.6 Hz), 4.51 dd (J = 4.6, 8.0 Hz), 4.05 q (J = 7.1 Hz), 3.98 dd (J = 4.0, 7.2 Hz), 3.56 dd (J = 4.4, 9.4 Hz), 3.50 dd (J = 5.8, 9.3 Hz), 3.06 m, 2.91 dd (J = 7.2, 14.0 Hz), 2.30 ddd (J = 5.3, 8.6, 13.9 Hz), 2.22 dd (J = 8.0, 13.2 Hz), 2.06 m, 2.03 s, 1.91 m, 1.76 o (J = 6.8 Hz), 0.86 d (J = 6.8 Hz), 0.81 d (J = 6.7 Hz).

MS (FAB; M/Z, relative intensity): 937 (P + 1, 100).

Example 101

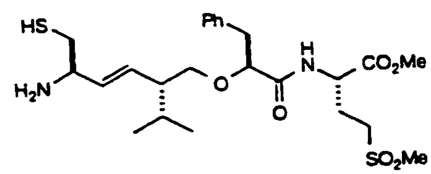
<u>Compound PE051</u>



^{1}H NMR (CD_3OD) δ: 8.12 d (J = 8.1 Hz), 7.19 - 7.29 m, 5.71 dd (J = 9.2, 15.6 Hz), 5.45 dd (J = 7.7, 15.6 Hz), 4.61 m, 4.00 dd (J = 4.7, 7.3 Hz), 3.81 q (J = 6.7 Hz), 3.71 s, 3.52 dd (J = 7.7, 15.6 Hz), 3.44 dd (J = 5.5, 9.1 Hz), 3.04 dd (J = 4.5, 13.9 Hz), 2.91 dd (J = 7.4, 13.9 Hz), 2.81 dd (J = 7.0, 14.2 Hz), 2.76 dd (J = 7.2, 13.2 Hz), 2.29 m, 2.04 s, 1.92 m, 1.77 o (J = 6.5 Hz), 0.91 d (J = 6.8 Hz), 0.81 d (J = 6.8 Hz).

Example 102

Compound PE061



^{1}H NMR (CD_3OD) δ: 8.07 d (J = 8.1 Hz), 7.20 - 7.30 m, 5.84 dd (J = 9.2, 15.5 Hz), 5.47 dd (J = 7.8, 15.5 Hz), 4.59 m, 4.04 dd (J = 4.4, 7.0 Hz), 3.82 q (J = 6.6 Hz), 3.74 s, 3.63 dd (J = 4.8, 9.3 Hz), 3.46 dd (J = 6.9, 9.2 Hz), 3.08 dd (J = 4.3, 14.1 Hz), 2.93 s, 2.77 - 2.84 m, 2.71 dd (J = 6.1, 14.0 Hz), 2.30 m, ~2.1 m, 1.74 o (J = 6.7 Hz), 0.87 d (J = 6.9 Hz), 0.84 d (J = 6.8 Hz).

Example 103

Bromide R001T

Triphenylphosphine (2.30 g, 8.78 mmol) was added to a solution of carbon tetrabromide (2.96 g, 8.92 mmol) in CH_2Cl_2 (25 mL) at 5 °C. The reaction was stirred for 10 min during which time it became dark yellow. A solution of alcohol **R019D** (1.281 g, 3.89 mmol) in CH_2Cl_2 (15 mL) was then added dropwise whereupon the reaction mixture became much lighter in color. The reaction was stirred at room temp for an additional 30 min, at which time TLC (eluting with 30% ethyl acetate:hexanes) indicated incomplete conversion to product. Additional quantities of triphenylphospine (1.08 g, 4.12 mmol) and carbon tetrabromide (1.41 g, 4.25 mmol) were added to ensure complete conversion and the color of the mixture returned to dark yellow. After stirring overnight, the reaction mixture was washed with water, dried over $MgSO_4$, filtered, concentrated *in vacuo*, and purified by FC, (eluting with 5%

ethyl acetate:hexanes) to afford bromide **R001T** (1.438 mg, 92%) as a colorless oil.

^1H NMR ($CDCl_3$) δ: 5.69 dd (J = 7.2, 15.2 Hz), 5.48 bs, 4.84 bs, 3.47 dd (J = 5.3, 9.9 Hz), 3.40 dd (J = 7.1, 9.9 Hz), 3.29 dd (J = 6.0, 11.7 Hz), 2.60 d (J = 11.7 Hz), 2.14 m, 1.82 m, 1.46 s, 0.92 d (J = 6.7 Hz), 0.88 d (J = 6.7 Hz).

Example 104

Thioacetate **R002T**

Potassium thioacetate (146 mg, 1.28 mmol) was added to a solution of bromide **R001T** (251 mg, 0.64 mmol) in DMF (1 mL). After stirring at room temp for 1 h, complete conversion to product was observed by TLC (eluting with 30% ethyl acetate:hexanes). The reaction was concentrated *in vacuo* and purified by FC (eluting with 5% ethyl acetate:hexanes), to afford thioacetate **R002T** (272 mg, 100%) as a yellow oil.

^1H NMR ($CDCl_3$) δ: 5.62 dd (J = 6.8, 14.0 Hz), 5.38 bs, 4.8 bs, 3.26 dd (J = 5.7, 12.0 Hz), 3.09 dd (J = 5.3, 13.4 Hz), 2.78 dd (J = 9.6, 13.9 Hz), 2.56 d (J = 13.4 Hz), 2.30 s, 1.98 m, 1.76 s, 1.44 s, 0.91 d (J = 6.7 Hz), 0.87 d (J = 6.7 Hz).

Example 105

Thiol **R003T**

Flame-dried potassium carbonate (170 mg, 0.6 mmol) was added to a solution of thioacetate **R002T** (124 mg, 0.3 mmol) in methanol degassed with argon (2 mL) and the reaction was stirred at room temp for 10 min. The reaction was acidified to pH 2.0 with 0.1N HCl and extracted with ethyl acetate. TLC (eluting with 20% ethyl acetate-hexanes) exhibited no disulfide formation. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in*

vacuo. The crude product was purified by FC (eluting with 2% ethyl acetate:hexanes) to give the free thiol **R003T** (79 mg, 72%) as a colorless oil.

^1H NMR ($CDCl_3$) δ: 5.66 dd (J = 6.8, 15.3 Hz), 5.37 bm, 4.86 bs, 3.29 dd (J = 6.1, 11.7 Hz), 2.60 d (J = 11.4 Hz), 2.51 m, 1.95 m, 1.76 s, 1.45 s, 0.90 d (J = 6.7 Hz), 0.86 d (J = 6.7 Hz).

Example 106

<u>Mesylate **R008T**</u>

Triethylamine (0.616 ml, 4.42 mmol) was added to a solution of methyl 2-(S)-hydroxy-3-phenylpropionate (0.5 g, 2.76 mmol) in CH_2Cl_2 (10 mL) at 0°C, followed by dropwise addition of mesyl chloride (0.32 mL, 4.14 mmol). After 10 min, the reaction was warmed to room temp. TLC (eluting with 10% diethyl ether:CH_2Cl_2) indicated complete conversion to product. The reaction was partitioned between saturated aq NH_4Cl (100 mL) and CH_2Cl_2 (100 ml) and then extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by FC (eluting with 10% ethyl acetate-hexanes) to afford desired mesylate **R008T** (614 mg, 86%) as a colorless oil.

^1H NMR ($CDCl_3$) δ: 7.2 ~ 7.4 m, 5.17 dd (J = 4.2, 8.9 Hz), 3.80 s, 3.30 dd (J = 4.1, 14.4 Hz), 3.13 dd (J = 8.9, 14.4 Hz), 2.77 s.

Example 107

Methyl ester R004T

Flame-dried potassium carbonate (138 mg, 1.0 mmol) was added to a solution of thiol R003T (168 mg, 0.502 mmol) and mesylate R008T (260 mg, 1.0 mmol) in argon degassed methanol (5 mL) and the reaction was stirred at room temp for 0.5 h. TLC (eluting with 30% ethyl acetate:hexanes) showed complete disappearance of starting thiol R003T. The reaction was quenched by addition of 0.1 *N* HCl solution and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The resulting crude product was purified by FC (eluting with 5% ethyl acetate:hexanes), to afford methyl ester R004T (96 mg, 39%) as a colorless oil.

^1H NMR ($CDCl_3$) δ: 7.18 - 7.30 m, 5.63 dd (J = 6.8, 15.2 Hz), 5.38 bs, 4.79 bs, 3.67 s, 3.66 s, 3.48 m, 3.25 m, 3.18 m, 2.94 m, 2.71 m, 2.57 m, 2.0 m, 1.58 s, 1.44 s, 0.85 m.

Example 108

Acid R005T

A solution of lithium hydroxide (45 mg, 1.89 mmol) in water (1 mL) was added to a solution of methyl ester R004T (96 mg, 0.189 mmol) in dioxane (1 mL) and the reaction was stirred vigorously overnight. TLC (eluting with 30% ethyl acetate:hexanes) indicated complete disappearance of starting methyl ester R004T. The reaction was acidified to pH 2.0 with 0.1 *N* HCl and extracted with ethyl acetate. The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo* to give acid R005T (98 mg, 100%) as a clear oil. The crude product was used in the next reaction directly without further purification.

^1H NMR ($CDCl_3$) δ: 7.20 - 7.30 m, 5.55 dd (J = 6.3,

15.2 Hz), 5.35 bm, 4.87 bm, 3.45 m, 3.23 m, 3.18 m, 2.92 m, 2.68 m, 2.56 m, 1.97 bm, 1.76 s, 1.65 m, 1.45 s, 0.86 d (J = 6.7Hz), 0.83 d (J = 6.8 Hz).

Example 109

Methyl ester **R006T**

A solution of acid **R005T** (98 mg, 198 μmol), methionine methyl ester hydrochloride (48 mg, 238 μmol), EDC (57 mg, 297 μmol), HOBT (28 mg, 208 μmol) and NMM (23μL, 208 μmol) in DMF (2 mL) was stirred at room temp overnight. The reaction mixture was diluted with ethyl acetate (50 mL), washed twice with water (50 mL), pH 7.2 phosphate buffer (50 mL) and brine (50 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo* to afford methyl ester **R006T** (106 mg, 78%) as a colorless oil. The crude product was used in the next reaction directly without further purification.

^1H NMR ($CDCl_3$) δ: 7.18 - 7.30 m, 7.20 m, 5.6 m, 5.34 bm, 4.8 bs, 4.66 m, 3.73 s, 3.72 s, 3.55 m, 3.43 t (J = 7 Hz), 3.23 m, 3.02 dd (J = 7.5 Hz), 2.92 m, 2.66 td (J = 13.5, 5 Hz), 2.54 m, 2.46 m, 2.32 m, 2.05 s, 2.03 s, 1.76 s, 1.44 s, 0.83 m.

Example 110

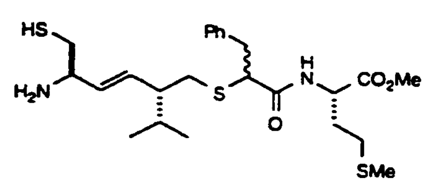
Disulfide R007T

Methoxycarbonylsulfenyl chloride (8.4 µL, 93.56 µmol) was added dropwise to a solution of thiazolidine R006T (61 mg, 95.47 µmol) in acetic acid (1 mL), DMF (0.1 mL) and water (0.05 mL) at 0°C. After stirring at 0°C for 25 min and room temp for 5 min, reverse phase HPLC (eluting with 0.15% TFA in 5% acetonitrile-water to 0.15% TFA in acetonitrile over 30 min) indicated complete disappearance of starting material R006T. The reaction was concentrated *in vacuo* and purified by preparative reverse phase HPLC. Disulfide R007T (59 mg, 90%) was obtained as a colorless oil.

^{1}H NMR ($CDCl_3$) δ: 7.20 - 7.28 m, 5.44 m, 5.38 bm, 5.17 bm, 4.66 m, 4.39 bm, 3.90 s, 3.73 s, 3.55 q (J = 6.5 Hz), 3.42 t (J = 10 Hz), 3.26 m, 3.02 m, 2.91 q (J = 8 Hz), 2.67 m, 2.49 m, 2.33 m, 2.05 s, 2.03 s, 1.93 m, 1.67 m, 1.45 s, 0.854 d (J = 6.7 Hz), 0.847 d (J = 6.7 Hz), 0.812 d (J = 6.7 Hz), 0.802 d (J = 6.8 Hz).

Example 111

Compound PT011



Tri-*n*-butylphosphine (0.107 mL, 0.428 mmol) was added to a solution of disulfide R007T (59 mg, 85.63 µmol) in THF (2 mL) and water (0.1 mL) and the reaction stirred at room temp for 0.5 h. Reverse phase HPLC (eluting with 0.15% TFA in 5% acetonitrile-water to 0.15% TFA in acetonitrile over 30 min) indicated complete conversion to product. The

reaction was concentrated *in vacuo* and the crude product was dissolved in Et_3SiH (1 mL). TFA (3 mL) was added and the reaction stirred at room temp for 0.5 h. Reverse phase HPLC (eluting with 0.15% TFA in 5% acetonitrile-water to 0.15% TFA in acetonitrile over 30 min) indicated complete conversion to product. The reaction was concentrated *in vacuo* and purified by preparative reverse phase HPLC. After one chromatography, the final product still contained residual amounts of tri-*n*-butylphosphine and a second purification was necessary. Compound **PT011** (8.1 mg, 15%) was obtained as a white solid of diastereomers after lyophilization from acetonitrile:H_2O (2:1).

^1H NMR (CD_3OD) δ: 7.17 - 7.28 m, 5.71 dd (J = 9.2, 15.4 Hz), 5.43 dd (J = 7.8, 15.7 Hz), 4.50 m, 3.83 q (J = 6.8 Hz), 3.70 s, 3.64 s, 3.6 m, 3.16 dd (J = 8.5, 13.8 Hz), 3.02 dd (J = 10.6, 13.2 Hz), 2.65 - 2.95 m, 2.61 dd (J = 9.4, 11.9 Hz), 2.47 m, 2.39 m, 2.1 m, 2.05 s, 1.97 s, 1.95 m, 1.75 m, 0.96 d (J = 6.8 Hz), 0.94 d (J = 6.9 Hz), 0.92 d (J = 6.9 Hz), 0.89 d (J = 6.8 Hz).

Example 112

<u>Methyl ester **R002M**</u>.

5-Formylsalicylic acid (50.67 g, 305.0 mmol) was dissolved in MeOH (1.0 L) at room temp, concentrated H_2SO_4 (10 mL) was added, and the reaction solution was heated at reflux under nitrogen for 24 h. The solution was allowed to cool to room temp and was then concentrated to give a moist solid. To this solid was added H_2O (200 mL), MeOH (10 mL), and EtOAc (600 mL). The phases were separated, and the EtOAc phase was washed successively with H_2O (200 mL), saturated $NaHCO_3$ (3 x 200 mL), H_2O (200 mL), and saturated NaCl (2 x 200 mL). The EtOAc was then dried over $MgSO_4$, filtered through K_2CO_3, and concentrated to give a solid.

This solid was crystallized from hot $MeOH/H_2O$ (1:1, vol:vol, 1.0 L each) to give light tan needles which were collected by filtration, washed with $MeOH/H_2O$ (1:1, vol:vol), and dried under vacuum to give 35.31 g (64%) of ester **R002M** as yellow-tan needles with a strong odor of wintergreen. (Piscopo, et al. *Farmaco.*, 1991, 46: 669-676). The following characteristic values were obtained by nuclear magnetic resonance spectroscopy:

^1H NMR ($CDCl_3$) δ: 11.38 s, 9.88 s, 8.38 d (J = 2.2 Hz), 8.00 dd (J = 2.1, 8.7 Hz), 7.10 d (J = 8.6 Hz), and 4.10 s.

Example 113

Triflate **R003M**

Ester **R002M** (35.31 g, 196.0 mmol) was dissolved in dry pyridine (150 mL) at room temp under nitrogen, and the solution was cooled to 0°C in an ice-water bath. Triflic anhydride (39.0 mL, 232 mmol) then was added over 15-20 minutes. The reaction solution was stirred at 0°C for 3 h, the bath was removed, and the solution was stirred for an additional 3 h. The reaction solution was diluted with Et_2O (1000 mL) and washed successively with H_2O (2 x 200 mL), 10% HCl (3 x 150 mL), H_2O (150 mL), and saturated NaCl (2 x 150 mL). The combined aqueous phases were back-extracted with Et_2O (2 x 200 mL), and these Et_2O extracts were washed successively with 10% HCl (200 mL), H_2O (100 mL), and saturated NaCl (100 mL). The combined Et_2O phases were dried over $MgSO_4/K_2CO_3$, filtered, and concentrated to afford a brown liquid which was purified by FC (eluting with EtOAc/hexanes) to furnish 45.49 g (74%) of triflate **R003M** as a faintly yellow liquid which solidified on standing. The following characteristic values were obtained by nuclear magnetic resonance spectroscopy:

^1H NMR ($CDCl_3$) δ: 10.09 s, 8.61 d (J = 2.2 Hz), 8.17 dd (J = 2.3, 8.4 Hz), 7.50 d (J = 8.5 Hz), and 4.02 s.

$^{19}F\{^1H\}$NMR ($CDCl_3$, $CFCl_3$ = 0.0 ppm) δ: -73.8 s.

Example 114

Aldehyde **R004M**

Triflate **R003M** (46.90 g, 150.2 mmol), benzeneboronic acid (40.42 g, 331.5 mmol), K_2CO_3 (31.34 g, 226.8 mmol), and $Pd(CH_2Ph)(Cl)(PPh_3)_2$ (3.4753 g, 4.5874 mmol) were dissolved in dry toluene (1000 mL) under argon at room temp. The resulting solution was heated to 100°C for 4 h and then allowed to cool to room temp. The reaction mixture was filtered through CELITE®, and the CELITE® was rinsed with EtOAc. The filtrate was concentrated to approximately 100-200 mL, and 600 mL of EtOAc was added. This solution was washed successively with H_2O (200 mL), saturated $NaHCO_3$ (200 mL), 0.01 *N* HCl (200 mL), pH 7.2 phosphate buffer (200 mL), and saturated NaCl (200 mL); dried over $MgSO_4$ with decolorizing carbon; filtered; and evaporated to give a yellow-orange sludge. Purification by FC (eluting with EtOAc/hexanes) gave 34.80 g (96%) of ester **R004M** as a colorless, viscous liquid. The following characteristic values were obtained by nuclear magnetic resonance spectrosopy:

^1H NMR ($CDCl_3$) δ: 10.09 s, 8.33 d (J = 1.8 Hz), 8.05 dd (J = 1.9, 7.9 Hz), 7.57 d (J = 7.9 Hz), 7.39 - 7.47 (m, 3H), 7.32 - 7.36 (m, 2H), and 3.70 (s, 3H).

Example 115

Compound **R005M**

A solution of 1.0 M KO^tBu/THF (20.0 mL, 20.0 mmol) was added via syringe to a suspension of (methoxymethyl)-triphenylphosphonium chloride (5.8071 g, 16.940 mmol) in THF

(80 mL) cooled to 0°C. The resulting orange solution was stirred at 0°C for 5 minutes, stirred at room temp for 1 h, and then cooled to 0°C. A solution of aldehyde **R004M** (3.2413 g, 13.491 mmol) in THF (10.0 mL) was added via syringe. The resulting yellow reaction solution was stirred overnight at room temp. The solution was diluted with EtOAc (100 mL); washed successively with pH 7.2 phosphate buffer (2 x 50 mL), H_2O (50 mL), and saturated NaCl (2 x 50 mL); dried over $NaSO_4$; filtered; and concentrated to give a liquid. Purification by FC gave 2.6216 g (72%) of intermediate **R005M** as a colorless liquid (1.4:1 *trans/cis* ratio). The following characteristic values were obtained by nuclear magnetic resonance spectroscopy:

^1H NMR ($CDCl_3$) δ: 7.96 d (J = 1.9 Hz), 7.76 dd (J = 1.9, 9.0 Hz), 7.67 d (J = 1.9 Hz), 7.26 - 7.41 (m, 5H), 7.15 d (J = 13.0 Hz), 6.22 d (J = 7.0 Hz), 5.85 d (J = 13.0 Hz), 5.27 d (J = 7.0 Hz), 3.82 s (*cis* isomer), 3.72 s (*trans* isomer), 3.63 s, and 3.63 s.

Example 116

Compound **R006M**

Intermediate **R005M**, (0.582 g, 2.168 mmol) was dissolved in 1,4-dioxane (28 mL) and H_2O (6 mL), and *p*-toluenesulfonic acid (0.081 g, 0.4258 mmol) was added. The solution was heated to 65°C for 12 h, then 75°C for 5 h, and finally 85°C for 8 h. The reaction solution was allowed to cool to room temp; diluted with EtOAc (150 mL); and washed successively with pH 7.2 phosphate buffer (50 mL), H_2O (50 mL), and saturated NaCl (50 mL). The solution then was dried over Na_2SO_4, filtered, and concentrated to give a viscous liquid which was purified by FC (eluting with EtOAc/hexanes) to give 0.376 g (68%) of intermediate **R006M** as a colorless,

viscous liquid. The following characteristic values were obtained by nuclear magnetic resonance spectroscopy:

^1H NMR ($CDCl_3$ δ: 9.82 t (J = 2.1 Hz), 7.70 s, 7.26 - 7.43 (m, 7H), 3.80 d (J = 2.0 Hz), and 3.64 (s, 3H).

Example 117

Compound R008M

A solution of R007M (L-cysteine methyl ester hydrochloride) (25.7009 g, 149.7372 mmol) in H_2O (200 mL) was cooled to 0°C, and $NaHCO_3$ (13.01 g, 154.9 mmol) and K_2CO_3 (21.85 g, 158.1 mmol) were added. Phosgene (20 wt% in toluene, 105 mL, 203 mmol) was then added dropwise. The resulting solution was stirred vigorously at 0 °C for approximately 2 h. The phases were separated, and the aqueous phase was evaporated to yield a white, granular solid. This solid was extracted with CH_2Cl_2 (4 x 100 mL). The combined CH_2Cl_2 extracts were dried over $MgSO_4$, filtered, and evaporated to give 17.6776 g (73%) of intermediate R008M as a colorless liquid which solidified on standing at -20 °C. For an alternative synthesis, see E. Falb, et al., *Synth. Commun.*, 23(20) 2839-44 (1993). The following characteristic values were obtained by nuclear magnetic resonance spectroscopy:

^1H NMR ($CDCl_3$) δ: 6.35 br s, 4.45 ddd (J = 0.7, 5.2, 8.2 Hz), 3.83 s, 3.72 dd (J = 8.2, 11.4 Hz), and 3.64 dd (J = 5.0, 11.4 Hz).

Example 118

Compound R009M

Intermediate R008M (17.6776 g, 109.68 mmol) was dissolved in dry EtOH (200 mL) at 0°C. $NaBH_4$ (6.0938 g, 161.08 mmol) was added portionwise under N_2. The resulting solution was stirred at 0°C for 1.5 h and then allowed to

warm to room temp. The reaction was quenched by addition of aqueous saturated NH_4Cl (30 mL) followed by vigorous stirring for 30 minutes. The mixture was filtered, and the filtrate was concentrated to give 17.6188 g (121%) of intermediate **R009M** as a syrup. The following characteristic values were obtained by nuclear magnetic resonance spectroscopy:

^1H NMR (CD_3OD) δ: 3.89 - 3.95 m, 3.49 - 3.63 m, and 3.28 dd (J = 5.6, 11.1 Hz).

Example 119

<u>Compound **R010M**</u>

Intermediate **R009M** (17.62 g, 132.31 mmol) was combined with dry pyridine (55 mL) at 0°C, and TsCl (35.4g, 185.7 mmol) was added portionwise under N_2. The resulting solution was stirred at 0°C for 4 h and then at room temp for 2.5 h. The pyridine was removed under vacuum to leave a thick sludge which was diluted with CH_2Cl_2 (250 mL) and washed with aqueous 2*N* HCl (4 x 50 mL, 1 x 100 mL). The combined aqueous washings were back-extracted with CH_2Cl_2 (2 x 50 mL). The combined CH_2Cl_2 phases were washed with H_2O (100 mL) and saturated NaCl (100 mL), dried over $MgSO_4$, filtered, and evaporated to give a light brown solid. This solid was dissolved in CH_2Cl_2 (approximately 100 mL), and hexane (approximately 300 mL) was added. This solution was concentrated to approximately 100 mL, and a solid precipitated. The solid was collected by filtration, washed with hexane, and dried under vacuum to give 28.1163 g (74%, 90% from intermediate **R008M**) of intermediate **R010M** as a tan solid. The following characteristic values were obtained by nuclear magnetic resonance spectroscopy:

^1H NMR ($CDCl_3$) δ: 7.80 d (J = 8.2 Hz), 7.39 d (J = 8.2 Hz), 6.20 br s, 4.09 - 4.15 m, 3.98 - 4.03 m, 3.52 - 3.56 m, 3.13 dd (J = 4.3, 11.5 Hz), and 2.47 s.

Example 120

<u>Compound R011M</u>

Intermediate **R010M** (27.8043 g, 96.761 mmol), sodium iodide (64.0 g, 427 mmol), and $NaHCO_3$ (0.420 g, 4.99 mmol) were combined in acetone (400 mL). The resulting solution was heated at reflux under N_2 for 12 h. The solution was cooled to room temp and filtered. The filtrate was evaporated, and the residue was dissolved in EtOAc (300 mL) and H_2O (100 mL). The phases were separated, and the EtOAc phase was washed with saturated Na_2SO_3 (2 x 75 mL) and saturated NaCl (100 mL). The combined aqueous phases were back-extracted with EtOAc (2 x 100 mL), and these EtOAc extracts were combined and washed with saturated NaCl (50 mL). The combined EtOAc phases were dried over $MgSO_4$ (with decolorizing carbon added), filtered, and evaporated to give a tan solid (22.8106 g, 97%), which was purified by FC (eluting with EtOAc/hexanes) to give 17.2634 g (74%) of intermediate **R011M** as a white, crystalline solid. The following characteristic values were obtained by nuclear magnetic resonance spectroscopy:

^1H NMR ($CDCl_3$) δ: 6.51 br s, 4.05 - 4.10 m, 3.61 dd (J = 7.5, 11.4 Hz), and 3.24 - 3.37 m.

Example 121

<u>Compound R012M</u>

Intermediate **R011M** (16.2294 g, 66.7712 mmol), triphenylphosphine (88.27 g, 336.5 mmol), and DMF (30 mL) were combined and heated to 100°C for 42 h. After cooling to room temp, the DMF was removed under vacuum to leave a semi-solid residue. This residue was repeatedly washed with

Et_2O to remove triphenylphosphine and then purified by FC (eluting with $MeOH/CHCl_3$) to give an off-white solid which was dried under vacuum at 80°C to give 28.55 g (85%) of intermediate **R012M** as a tan solid. The following characteristic values were obtained by nuclear magnetic resonance spectroscopy and optical rotation:

^1H NMR (CD_3OD/D_2O) δ: 7.74 - 7.95 m, 4.81 br s, 4.39 - 4.46 m, 3.83 - 4.02 m, 3.49 - 3.54 m, and 2.98 dd (J = 3.6, 8.1 Hz).

$^{13}C\{^1H\}$ NMR (CD_3OD/D_2O) δ: 178.3, 137.5, 135.4 d (J = 10.2 Hz), 132.5 d (J = 12.7 Hz), 119.4 d (J = 86.9 Hz), 52.0, 37.9 d (J = 7.3 Hz), and 28.7 d (J = 52.1 Hz).

$^{31}P\{^1H\}$ NMR (CD_3OD/D_2O) δ: 24.0(s).

$[\alpha]^{24}_{589}$ = +18.39 (c=0.0255, MeOH).

$C_{22}H_{21}INOPS$

Anal. Calcd. :

C, 52.29; H, 4.19; I, 25.11; N, 2.77; S, 6.34.

Found:

C, 52.30; H, 4.20; I, 25.81; N, 2.81; S, 6.26.

Example 122

Compound **R013M**

Intermediate **R012M** (0.7720 g, 1.5277 mmol) was suspended in dry THF (7 mL) and cooled to approximately -42°C. To this solution, *n*-BuLi in hexane (0.600 mL, 1.52 mmol) was added via syringe, followed by LiHMDS in THF (1.52 mL, 1.52 mmol). The resulting red-orange solution was stirred at -42°C for 1 h. A solution of intermediate **R006M** (0.3755 g, 1.4767 mmol) in THF (2 mL) was added via syringe,

and the syringe was rinsed with THF (2 x 0.5 mL). The reaction mixture was stirred at -42°C for 1 h and then at room temp for 1.75 h. The reaction was quenched with 5 mL of saturated NH_4Cl, and diluted with EtOAc (150 mL) and H_2O (50 mL). The phases were separated, and the EtOAc phase was washed successively with pH 7.2 phosphate buffer (50 mL) and saturated NaCl (2 x 50 mL), dried over $MgSO_4$, filtered, and concentrated to give an orange oil. Purification by FC (eluting with EtOAc/hexanes) gave 0.1589 g of intermediate **R013M cis** and 0.2341 g of intermediate **R013M trans** as colorless oils. The following characteristic values were obtained by nuclear magnetic resonance spectroscopy:

<u>Compound **R013M cis**</u>

^1H NMR ($CDCl_3$) δ: 7.60 s, 7.26 - 7.42 m, 5.92 br s, 5.87 dt (J = 7.8, 10.5 Hz), 5.70 app t (J = 9.9 Hz), 4.86 app q (J = 8.2 Hz, 1H), 3.63 s, 3.50 - 3.60 m, 3.46 dd (J = 7.0, 10.8 Hz), and 3.24 dd (J = 8.5, 10.8 Hz).

<u>Compound **R013M trans**</u>

^1H NMR ($CDCl_3$) δ: 7.82 s, 7.18 - 7.41 m, 6.30 br s, 5.92 dt (J = 7.2, 14.3 Hz), 5.59 dd (J = 7.5, 15.2 Hz), 4.37 q (J = 7.4 Hz), 3.61 s, 3.47 dd (J = 7.3, 11.0 Hz), 3.44 br d (J = 6.4 Hz), and 3.17 dd (J = 7.5, 10.9 Hz).

Example 123

<u>Compound **R014M**</u>

Intermediate **R013M trans** (0.2341 g, 0.6623 mmol), BOC_2O (0.1765 g, 0.8087 mmol), and DMAP (0.0088 g, 0.072 mmol) were combined in THF (4.0 mL) and stirred for 3 h at room temp. The reaction solution was diluted with EtOAc (70 mL), washed successively with H_2O (2 x 25 mL) and saturated NaCl (2 x 25 mL), dried over $MgSO_4$, filtered, and evaporated to give an oil. Purification by FC (eluting with

EtOAc/hexanes) gave 0.2352 g (78%) of intermediate **R014M** as a colorless oil. The following characteristic values were obtained by nuclear magnetic resonance spectroscopy:

^{1}H NMR ($CDCl_3$) δ: 7.62 d (J = 1.6 Hz), 7.21-7.57 m, 5.94 dt (J = 7.3, 14.6 Hz), 5.79 dd (J = 6.9, 15.3 Hz), 4.97 t (J = 7.2 Hz), 3.60-3.68 m, 3.63 s, 3.48 d (J = 6.7 Hz), 2.92 dd (J = 1.4, 11.0 Hz), and 1.43 s.

Example 124

Compound **R015M**

Intermediate **R014M** (1.8280 g, 4.030 mmol) was dissolved in MeOH, and $CsHCO_3$ (0.797 g, 4.110 mmol) and Cs_2CO_3 (0.2638 g, 0.810 mmol) were added. The resulting solution was stirred at room temp for 18 h. Additional Cs_2CO_3 (0.3787 g, 1.162 mmol) was added, and stirring was continued for 27 h. The reaction solution was diluted with EtOAc (350 mL); washed successively with 0.01 N HCl (150 mL), H_2O (100 mL), pH 7.2 phosphate buffer (100 mL), and saturated NaCl (2 x 100 mL); dried over $MgSO_4$; filtered; and concentrated to give a viscous liquid. This liquid was diluted with THF (15 mL) and H_2O (5 mL), and then nBu$_3$P (2.0 mL, 8.027 mmol) was added. The resulting solution was stirred at room temp for approximately 2 h. The volatiles were removed under vacuum, and the residue was purified by FC (eluting with EtOAc/hexanes) to give 0.8216 g (48%) of intermediate **R015M** as an oily foam.

^{1}H NMR ($CDCl_3$) δ: 7.64 d (J = 1.5 Hz), 7.26-7.41 m, 5.85 ddt (J = 1.4, 6.8, 15.5 Hz), 5.47 dd (J = 5.6, 15.4 Hz), 4.91 br s, 4.40 br s, 3.63 s, 3.47 d (J = 6.7 Hz), 2.66 - 2.81 m, 1.44 s, and 1.35 dd (J = 7.6, 9.4 Hz).

Example 125

Compound R016M

Intermediate **R015M** (0.3710 g, 0.8677 mmol) and triphenylmethanol (0.5655 g, 2.1722 mmol) were combined and dissolved in dry Et_2O at 0°C. $BF_3 \bullet OEt_2$ (0.215 mL, 1.748 mmol) was added, and the solution was stirred at 0°C for 1 h. The solution was diluted with Et_2O (70 mL); washed successively with saturated $NaHCO_3$ (25 mL), H_2O (25 mL), and saturated NaCl (2 x 25 mL); dried over Na_2SO_4; filtered; and evaporated to give a solid. Purification by FC (eluting with EtOAc/hexanes) gave 0.4687 g (81%) of intermediate **R016M** as a solid/foam. The following characteristic values were obtained by nuclear magnetic resonance spectroscopy:

^1H NMR ($CDCl_3$) δ: 7.60 d (J = 1.6 Hz), 7.18 - 7.42 m, 5.67 ddt (J = 0.8, 7.2, 15.3 Hz), 5.37 dd (J = 5.5, 15.3 Hz), 4.61 br s, 4.19 br s, 3.60 s, 3.39 d (J = 6.7 Hz), 2.32 - 2.48 m, and 1.41 s.

Example 126

Compound R017M

Intermediate **R016M** (0.4687 g, 0.7007 mmol) was dissolved in MeOH (15.0 mL). LiOH (0.3985 g, 16.6388 mmol) and H_2O (3.0 mL) were added to give a milky solution. This solution was heated to 60°C for 12 h and then allowed to cool to room temp. The reaction solution was acidified to approximately pH 2 with 1 N $KHSO_4$ (25 mL), and diluted with EtOAc (70 mL) and H_2O (25 mL). The phases were separated, and the EtOAc phase was washed with saturated NaCl (2 x 30 mL), dried over $MgSO_4$, filtered, and evaporated to give an oil. Evaporation from CH_2Cl_2/hexanes gave 0.4300 g (93%) of intermediate **R017M** as a colorless solid. The following characteristic values were obtained by nuclear magnetic resonance spectroscopy:

^1H NMR (CD_3OD) δ: 7.56 s, 7.08 - 7.38 m, 5.58 - 5.66 m, 5.33 dd (J = 6.6, 15.3 Hz, 4.80 br s, 3.94 br s, 3.37 d (J = 6.7 Hz), 2.40 dd (J = 7.7, 12.1 Hz), 2.17 dd (J = 6.2, 12.2 Hz) and 1.41 s.

Example 127

Compound **R018M**

Intermediate **R017M** (0.0740 g, 0.1128 mmol), L-methionine PNB ester hydrochloride (0.0436 g, 0.1359 mmol), CMC (0,0823 g, 0.1943 mmol), HOBT (0.0156 g, 0.1154 mmol), NMM (0.013 mL, 0.1182 mmol), and DMF (1.0 mL) were combined, and the resulting solution was stirred at room temp for 72 h. The reaction solution was diluted with EtOAc (75 mL); washed successively with H_2O (2 x 25 mL), pH 7.2 phosphate buffer (25 mL), H_2O (25 mL), and saturated NaCl (2 x 25 mL); dried over $MgSO_4$; filtered; and evaporated to give an oil. Evaporation from CH_2Cl_2/hexanes gave 0.104 g (100%) of intermediate **R018M** as a solid. The following characteristic values were obtained by nuclear magnetic resonance spectroscopy:

^1H NMR (CD_3OD) δ: 8.22 d (J = 8.7 Hz), 7.18 - 7.48 m, 5.87 d (J = 7.6 Hz), 5.65 ddt (J = 0.7, 7.2, 15.3 Hz), 5.38 dd (J = 5.5, 15.2 Hz), 5.17 q (J = 12.6 Hz), 4.63 - 4.73 m, 4.61 br s, 4.18 br s, 3.38 d (J = 6.8 Hz), 2.30 - 2.48 m, 1.88 - 2.05 m, 1.96 s, 1.68 - 1.78 m, and 1.41 s.

Example 128

Compound **R019M**

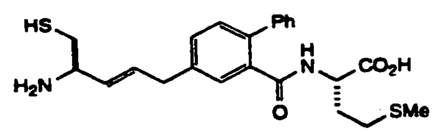
Intermediate **R018M** (0.1040 g, 0.1128 mmol) was dissolved in THF (6.0 mL) at room temp, and a solution of $Na_2S{\bullet}9H_2O$ (0.5898 g, 2.4557 mmol) in H_2O (2.0 mL) was added. The resulting solution was stirred vigorously at room temp for 2.5 h, and the reaction was quenched with TFA (0.400 mL) and evaporated. The residue was dissolved in MeOH,

filtered, and purified by RP HPLC to give 0.0633 g (71%) of intermediate **R019M** as a colorless solid. The following characteristic values were obtained by nuclear magnetic resonance spectroscopy:

^{1}H NMR (CD_3OD) δ: 7.17 - 7.44 m, 5.87 d (J = 7.6 Hz), 5.61 dt (J = 7.2, 14.3 Hz), 5.33 dd (J = 6.5, 15.3 Hz), 4.46 - 4.50 m, 3.94 br s, 3.37 d (J = 6.6 Hz), 2.40 dd (J = 7.6, 12.22 Hz), 2.10 - 2.22 m, 1.92-2.06 m, 1.99 s, 1.72 - 1.82 m, and 1.40 s.

Example 129

Compound **PM061**



Intermediate **R019M** (0.0633 g, 0.08043 mmol) and triisopropylsilane (0.400 mL, 1.9525 mmol) (or triethylsilane) were combined, and TFA (1.5 mL) was added. After 2 h, the reaction mixture was evaporated to leave a solid residue which then was dissolved in MeOH, filtered, and purified by RP HPLC to give 0.371 g of compound **PM061** (TFA salt). Compound **PM061** was dissolved in MeOH (or CH_3CN) (10 mL), and 1 *N* HCl (0.400 mL) was added. Evaporation and lyophilization from H_2O/CH_3CN gave 0.0273 g (71%) of compound **PM061** (HCl salt) as a colorless solid. The following characteristic values were obtained by nuclear magnetic resonance spectroscopy:

^{1}H NMR (CD_3OD) δ: 7.30 - 7.44 m, 6.14 dt (J = 7.2, 14.4 Hz), 5.57 dd (J = 8.0, 15.4 Hz), 4.46 br dd (J = 3.5, 9.6 Hz),

3.87 q (J = 6.8 Hz), 3.55 d (J = 6.5 Hz), 2.86 dd (J = 6.2, 14.2 Hz), 2.77 dd (J = 6.4, 14.2 Hz), 2.04 - 2.12 m, 1.92 - 2.00 m, 1.99 s, and 1.70 - 1.80 m.

Example 130

Compound **R020M**

Intermediate **R017M** (0.0570 g, 0.0869 mmol), *N,O*-dimethylhydroxylamine hydrochloride (0.0178 g, 0.1825 mmol), CMC (0.0588 g, 0.1388 mmol), HOBT (0.0136 g, 0.1006 mmol), NMM (0.011 mL, 0.1000 mmol), and DMF (1.0 mL) were combined, and the resulting solution was stirred at room temp overnight (approximately 16 h). The reaction solution was diluted with EtOAc (70 mL); washed successively with H_2O (2 x 30 mL), pH 7.2 phosphate buffer (30 mL), H_2O (30 mL), and saturated NaCl (30 mL); dried over $MgSO_4$; filtered; and evaporated to give an oil. Purification by FC eluting with EtOAc/hexanes gave 0.0504 g (83%) of intermediate **R020M** as a white solid. (Note: this compound exhibits rotational isomerism in the ^1H NMR at room temp.) The following characteristic values were obtained by nuclear magnetic resonance spectroscopy:

^1H NMR ($CDCl_3$) δ: 7.18 - 7.45 m, 5.64-5.72 m, 5.37 dd (J = 5.4, 15.6 Hz), 4.60 br s, 4.18 br s, 3.49 br s, 3.38 d (J = 6.7 Hz), 3.20 br s, 3.08 br s, 2.63 br s, 2.30 - 2.48 m, and 1.42 s.

Example 131

Compound **R021M**

Intermediate **R020M** (0.0504 g, 0.07211 mmol) was dissolved in Et_2O (4 mL) at 0°C under argon, and $LiAlH_4$ (0.0062 g, 0.163 mmol) was added to the solution all at once. After 30 minutes, the reaction was quenched by the addition of MeOH (0.5 mL) at 0°C. To this solution, saturated aqueous sodium potassium tartrate solution (1 mL)

was added, and the resulting mixture was stirred vigorously at room temp for 1 h. The mixture was filtered through CELITE®, and the filtrate was diluted with EtOAc (70 mL), washed successively with H_2O (2 x 25 mL) and saturated NaCl (2 x 25 mL), dried over Na_2SO_4, filtered, and concentrated to give 0.0420 g (91%) of intermediate **R021M** as an oil. The following characteristic values were obtained by nuclear magnetic resonance spectroscopy:

^1H NMR ($CDCl_3$) δ: 9.96 s, 7.81 d (J = 1.7 Hz), 7.19 - 7.50 m, 5.67 dt (J = 7.6, 15.2 Hz), 5.39 dd (J = 5.6, 15.3 Hz), 4.61 br s, 4.18 br s, 3.42 d (J = 6.8 Hz), 2.32 - 2.48 m, and 1.41 s.

Example 132

Compound **R022M**

Intermediate **R021M** (0.0420 g, 0.06564 mmol), L-methionine methyl ester hydrochloride (0.0436 g, 0.1359 mmol), EtOH (0.5 mL), and DMF (0.5 mL) were combined. To this solution was added $Na(CN)BH_3$ (0.0160 g, 0.2546 mmol), and the resulting mixture was stirred at room temp under argon for 6 h. The reaction solution was diluted with EtOAc (70 mL); washed successively with H_2O (2 x 30 mL), pH 7.2 phosphate buffer (30 mL), H_2O (30 mL), and saturated NaCl (2 x 30 mL); dried over $MgSO_4$; filtered; and evaporated to give an oil. Purification by FC (eluting with EtOAc/hexanes) gave 0.0400 g (77%) of intermediate **R022M** as a colorless oil. The following characteristic values were obtained by nuclear magnetic resonance spectroscopy:

^1H NMR ($CDCl_3$) δ: 7.09 - 7.43 m, 5.69 ddt (J = 1.2, 7.0, 14.0 Hz), 5.39 dd (J = 5.5, 15.3 Hz), 4.67 br s, 4.22 br s, 3.68 d (J = 12.4 Hz), 3.60 s, 3.56 d (J = 12.4 Hz), 3.37 d

(J = 6.9 Hz), 3.27 - 3.30 m, 2.45 - 2.58 m, 2.32 - 2.48 m, 2.04 s, 1.70 - 1.91 m, and 1.41 s.

Example 133

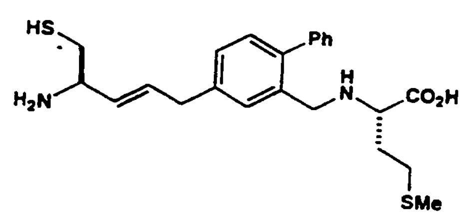
Compound R023M

Intermediate **R022M** (0.0221 g, 0.0281 mmol) was dissolved in MeOH (6.0 mL), 1,4-dioxane (1.5 mL), and H_2O (2.0 mL), and LiOH (0.0212 g, 0.8852 mmol) was added to the solution which then was stirred at room temp 24 h. The reaction solution was acidified with TFA (0.070 mL), and the volatiles were evaporated to give approximately 0.0249 g (100%) of intermediate **R023M** as a solid foam. The following characteristic values were obtained by nuclear magnetic resonance spectroscopy:

^1H NMR (CD_3OD) δ: 7.13 - 7.47 m, 5.58 - 5.62 m, 5.30 dd (J = 6.4, 15.3 Hz), 4.15 - 4.26 m, 3.90 - 3.95 br m, 3.72 - 3.75 m, 2.35 - 2.47 m, 2.14 - 2.19 m, 1.92 - 2.05 m, 1.92 s, and 1.36 s.

Example 134

Compound PM121



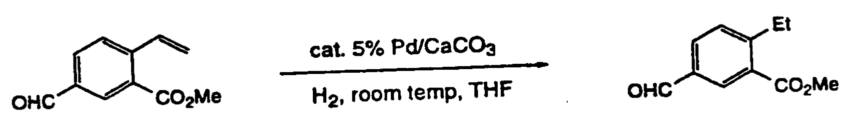
Intermediate **R023M** (approximately 0.0249 g, 0.02808 mmol) and triethylsilane (0.140 mL, 0.8765 mmol) were combined, and TFA (1.5 mL) was added. After 40 min, the reaction mixture was diluted with CH_3CN and purified by RP HPLC to give 0.0174 g of compound **PM121** (2TFA salt) which then was dissolved in CH_3CN (10 mL) and to which 1 *N* HCl (0.150 mL) was added. Evaporation, and

lyophilization from H_2O/CH_3CN gave 0.0110 g (78%) of compound **PM121** (2HCl salt) as a colorless solid. The following characteristic values were obtained by nuclear magnetic resonance spectroscopy:

^1H NMR (CD_3OD) δ: 7.59 s, 7.33 - 7.52 m, 6.17 dt (J = 7.2, 14.4 Hz), 5.63 dd (J = 8.0, 15.4 Hz), 4.34 br s, 3.87 - 3.92 m, 3.59 d (J = 6.0 Hz), 2.89 dd (J = 6.3, 14.2 Hz), 2.81 dd (J = 6.4, 14.1 Hz), 2.46 - 2.56 m, 2.01 - 2.15 m, and 2.03 s.

Example 135

Compound R025M (Eq. 1)



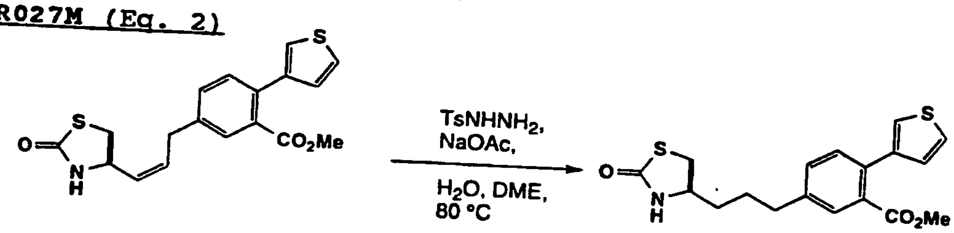
R024M **R025M**

Intermediate **R024M** (0.465 g, 2.43 mmol) was dissolved in THF (28 mL) under argon, and 5% $Pd/CaCO_3$ (0.094 g, 0.94 mmol, ca. 0.05 mmol Pd) was added. The solution was stirred under H_2 at room temp. for 30 min. The reaction solution was diluted with EtOAc and filtered through CELITE®. Evaporation gave 0.427 g of intermediate **R025M** (91%) as a colorless oil.

^1H NMR ($CDCl_3$) δ: 10.01 s, 8.37 d (J = 1.8 Hz), 7.95 d (J = 1.7, 8.0 Hz), 7.46 d (J = 7.9 Hz), 3.94 s, 3.07 q (J = 7.5 Hz), and 3.64 t (J = 7.6 Hz).

Example 136

Compound R027M (Eq. 2)



R026M

R027M

Intermediate R026M (0.827 g, 2.300 mmol) and $TsNHNH_2$ (6.521 g, 35.018 mmol) were dissolved in DME (60 mL) under N_2. The resulting solution was heated to 80 °C, and a solution of $NaOAc \cdot 3H_2O$ (6.293 g, 46.246 mmol) in H_2O (30 mL) was added dropwise over 6.5 h. The mixture was allowed to cool to room temp, diluted with H_2O (70 mL), and extracted with CH_2Cl_2 (3 x 60 mL). The combined CH_2Cl_2 layers were washed with saturated NaCl (50 mL), dried over Na_2SO_4, filtered, and concentrated to give an oil. Purification by FC (eluting with ethyl acetate/hexanes) gave 0.538 (65%) of R027M as a colorless oil.

^1H NMR ($CDCl_3$) δ: 7.56 - 7.58 m, 7.22 - 7.37 m, 7.07 dd (J = 1.4, 4.9 Hz), 5.74 br s 1H, 3.85 - 3.91 m, 3.72 s, 3.47 dd (J = 7.1, 10.9 Hz), 3.11 dd (J = 7.2, 10.9 Hz), 2.72 br t (J = 6.8 Hz), and 1.66 - 1.73 m.

Example 137

Iodoolefin R028M

Freshly distilled THF (10 mL) was added to $CrCl_2$ (300 mg, 2.43 mmol) under argon at 0 °C. A solution of aldehyde R004M (97.3 mg, 0.405 mmol) and iodoform (322.5 mg, 0.819 mmol) in freshly distilled THF (5 mL) was added dropwise to the $CrCl_2$ solution and the resulting mixture stirred for 3.5 h at 0 °C. TLC indicated complete loss of starting material and conversion to a new, less polar

product. pH 7.0 phosphate buffer concentrate (10 mL) was added and the mixture allowed to warm to room temp. Saturated aq NH_4Cl (10 mL) was added and the mixture allowed to stir for 10 min. The resulting suspension was filtered through CELITE®, and the filter cake was washed well with several rinses of ethyl acetate. The resulting mixture was diluted further with ethyl acetate, shaken, and the aqueous phase decanted. The organic phase was washed further with water, dried with brine, dried with $MgSO_4$, filtered, and concentrated to a brown residue (200.3 mg). After purification by FC (eluting with 15% ethyl acetate-hexanes), pure iodoolefin **R028M** was obtained as a pale yellow solid (145.8 mg, 99%).

^1H NMR ($CDCl_3$) δ: 7.75 d (J = 1.7 Hz), 7.48 d (J = 15.1 Hz), 7.3 - 7.4 m, 6.98 d (J = 15.0 Hz), 3.54 s.

Example 138

Alcohols R029M

$CrCl_2$ (240 mg, 1.953 mmol) was added all at once to a solution of aldehyde **R015D** (252.7 mg, 1.03 mmol) and iodoolefin **R028M** (119.1 mg, 0.327 mmol) stirring in DMSO (3 mL) in a dry box. Next, $Ni(COD)_2$ (3 mg, 0.011 mmol) was added to the above mixture and the resulting suspension stirred for 6 h at ambient temperature. The reaction was removed from the dry box and quenched by addition of saturated aq NH_4Cl (30 mL), CH_2Cl_2 (50 mL) was added, and the two phase mixture stirred at high speed for 15 min. The resulting two homogenous phases were transferred to a separatory funnel and separated. The aqueous layer was extracted twice with CH_2Cl_2 and the combined organic extracts washed twice with water, dried with $MgSO_4$, filtered, and concentrated to a yellow oil (345.5 mg). After purification by preparative TLC (eluting with 20% ethyl

acetate:hexanes), the desired diastereomeric mixture of alcohols **R029M** was obtained as a transparent oil (67.2 mg, 47%). NMR data for alcohols **R029M** is complicated by extensive rotational isomerism on the NMR time scale.

^{1}H NMR ($CDCl_3$) δ: 7.83 d (J = 9.3 Hz), 7.82 d (J = 8.7 Hz), 7.54 d (J = 8.0 Hz), 7.54 d (J = 7.9 Hz), 7.26 – 7.39 m, 6.70 d (J = 15.8 Hz), 6.67 (J = 15.5 Hz), 6.40 b dd (J = 2.3, 13.7 Hz), 6.33 dd (J = 7.4, 15.9 Hz), 3.63 s, 3.18 m, 3.03 d (J = 12.1 Hz), 2.81 d (J = 12.2 Hz), 1.84 m, 1.80 s, 1.78 s, 1.52 s, 1.42 s.

Example 139

<u>Trifluoroacetates R030M</u>

An excess of triethylamine (0.189 mL, 1.356 mmol) and trifluoroacetic anhydride (0.096 mL, 0.680 mmol) was added to a solution of alcohols **R029M** (65.5 mg, 0.135 mmol) in freshly distilled CH_2Cl_2 (5.0 mL). After 20 min, the reaction mixture was diluted with ether, and washed twice with pH 7.0 phosphate buffer concentrate, once with 0.1 N HCl, dried with $MgSO_4$, filtered, and concentrated to a crude oil (65.1 mg). Purification by preparative TLC (eluting with 20% ethyl acetate:hexanes) afforded impure trifluoroacetates **R030M** (R_f = 0.54, 39.6 mg, 50%) along with recovered **R029M** (R_f = 0.12, 18.1 mg, 27%).

Example 140

<u>Ester R031M</u>

A 2 M solution of iPrMgCl in THF (0.332 mL, 0.663 mmol) was dripped slowly into a suspension of CuCN (29.7 mg, 0.332 mmol) in freshly distilled THF (3.0 mL) stirring rapidly at -40 °C. After the addition had been completed the mixture was allowed to warm to 0 °C and stir for 40 min. The resulting dark solution was then recooled to -78 °C. An impure solution of trifluoroacetates **R030M** containing some

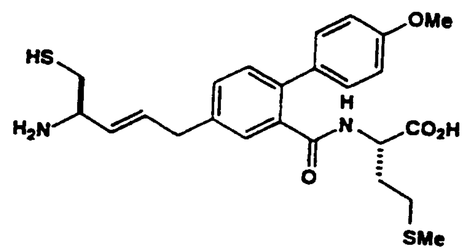
hydrolyzed alcohol (39 mg, ~0.067 mmol) in THF (1 mL) was added dropwise at -78 °C to the dark solution prepared above. The resulting mixture was stirred for 30 min and then quenched by addition of saturated aq NH_4Cl, (2 mL) warmed to room temp, NH_4OH (1 mL) and ether (20 mL). After stirring for 15 min, two homogeneous phases developed. The organic phase was decanted and washed with water, washed with pH 7.0 phosphate buffer concentrate, dried with $MgSO_4$, filtered, and concentrated to a clear oil (32.5 mg). After purification by preparative TLC (eluting with 10% ethyl acetate:hexanes, the pure ester **R031M** (9.9 mg, 29%) was obtained.

NMR data for alcohols **R029M** is complicated by extensive rotational isomerism on the NMR time scale. The rotational isomers (i, ii) are clearly distinguishable at -60 °C.

^{1}H NMR ($CDCl_3$), -60 °C δ: 7.63 s & 7.57 s, 7.26 - 7.43 m, 5.87 dd (i, J = 10.2, 14.7 Hz), 5.74 dd (i, J = 8.9, 14.9 Hz), 5.68 dd (ii, J = 7.2, 15.0 Hz), 5.61 dd (ii, J = 9.6, 14.5 Hz), 4.83 (i, m), 4.67 (ii, m), 3.69 s, 3.66, 3.24 t (ii, J = 6.0 Hz), 3.19 t (i, J = 5.9 Hz), 2.85 t (ii, J = 9.6 Hz), 2.79 t (i, J = 10.1 Hz), 2.52 d (J = 11.7 Hz), 1.92 br m, 1.82 s, 1.73 s, 1.70 s, 1.46 s, 1.35 s, 0.99 d (J = 5.8 Hz), 0.90 d (J = 5.9 Hz), 0.72 d (J = 6.0 Hz), 0.68 d (J = 6.0 Hz).

Example 141

Compound PM011

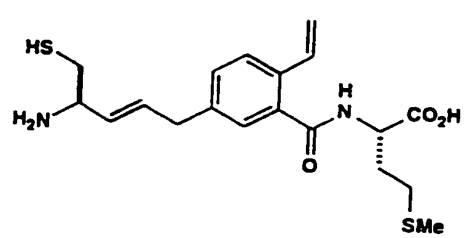


Compound PM011 was prepared in the same manner as that described in Scheme VIII, but 4-methoxybenzeneboronic acid and DMF were used in place of benzeneboronic acid and toluene in step 3, and L-methionine methyl ester hydrochloride was used in step 11 in place of L-methionine PNB ester hydrochloride, and the subsequent $Na_2S \cdot 9H_20$ step was replaced with a $LiOH/MeOH/H_20$ hydrolysis. The following characteristic values were obtained by nuclear magnetic resonance spectroscopy:

^{1}H NMR (CD_3OD) δ: 7.34 - 7.41 m, 6.98 d (J = 8.7 Hz), 6.16 dt (J = 7.1, 14.2 Hz), 5.59 dd (J = 8.0, 15.4 Hz), 4.49 - 4.52 m, 3.89 q (J = 7.0 Hz), 3.85 s, 3.56 d (J = 6.9 Hz), 2.88 dd (J = 6.2, 14.1 Hz), 2.79 dd (J = 6.4, 14.2 Hz), 2.06 - 2.19 m, 1.94 - 2.01 m, 2.01 s, and 1.72 - 1.84 m.

Example 142

Compound PM012



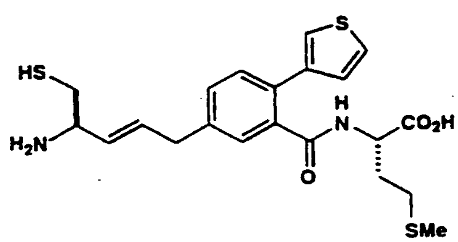
Compound PM012 was prepared in the same manner as that described in Scheme VIII, but tetravinyltin (with LiCl in

DMF) was used in place of benzeneboronic acid in step 3, and L-methionine t-butyl ester hydrochloride was used in step 11 in place of L-methionine PNB ester hydrochloride, and the subsequent $Na_2S \bullet 9H_2O$ step was omitted.

^1H NMR (CD_3OD) δ: 8.66 d (J = 7.6 Hz), 7.61 - 7.64 m, 7.14 - 7.36 m, 7.01 dd (J = 11.0, 17.5 Hz), 6.07 - 6.12 m, 5.77 d (J = 17.4 Hz), 5.49 - 5.55 m, 5.29 d (J = 11.7 Hz), 4.71 - 4.75 m, 3.85 q (J = 7.3 Hz), 3.49 - 3.59 m, 2.51 - 2.90 m, 2.13 - 2.24 m, 2.11 s, and 1.98 - 2.11 m.

Example 143

Compound PM021

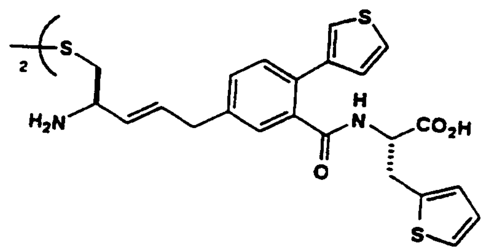


Compound PM021 was prepared in the same manner as that described in Scheme VIII, but 3-thiopheneboronic acid was used in place of benezeneboronic acid in step 3, and L-methionine t-butyl ester hydrochloride was used in step 11 in place of L-methionine PNB ester hydorchloride, and the subsequent $Na_2S \bullet 9H_20$ step was omitted. The following chracteristic values were obtained by nuclear magnetic resonance spectorscopy:

^1H NMR (CD_3)D) δ: 7.45 - 7.53 m, 7.37 - 7.39 m, 7.24 d (J = 4.8 Hz), 6.15 dt (J = 7.2, 14.4 Hz), 5.58 dd (J = 8.0, 15.4 Hz), 4.59 br dd (J = 4.0, 9.5 Hz), 3.88 q (J = 6.8 J Hz), 3.56 d (J = 6.5 Hz), 2.87 dd (J = 6.0, 13.8 Hz), 2.79 dd (J = 6.2, 14.1 Hz), 2.29 - 2.35 m, 2.18 - 2.25 m, 2.03 - 2.12 m, 2.06 s, and 1.82 - 1.91 m.

Example 144

Compound PM022

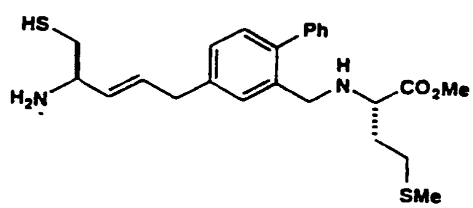


Compound **PM022** was prepared from compound **PM152** by exposure to air and was purified by RP HPLC.

^1H NMR (CD_3OD) δ: 7.21 - 7.43 m, 7.11 dd (J = 1.3, 4.0 Hz), 6.94 dd (J = 3.4, 5.1 Hz), 6.82 d (J = 2.9 Hz), 5.99 dt (J = 7.2, 14.4 Hz), 5.48 dd (J = 8.3, 15.4 Hz), 4.75 dd (J = 4.7, 9.1 Hz), 3.99 q (J = 7.3 Hz), 3.44 d (J = 5.7 Hz), 3.39 - 3.50 m, 3.22 dd (J = 9.2, 14.9 Hz), and 3.01 d (J = 6.5 Hz).

Example 145

Compound PM031



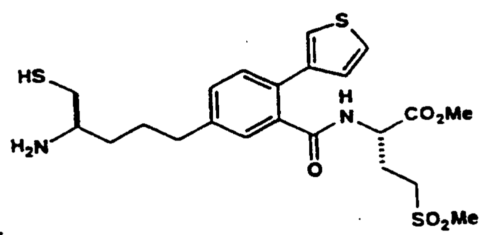
Intermediate **R022M** (approximately 0.0176 g, 0.02236 mmol) and triethylsilane (0.050 mL, 0.3130 mmol) were combined, and TFA (1.0 mL) was added at 0°C. After approximately 2 h, the reaction mixture was diluted with CH_3CN and purified by RP HPLC to give 0.0156 g of compound **PM031** (2TFA salt). Compound **PM031** was dissolved in CH_3CN (10 mL), and 1 *N* HCl (0.150 mL) was added to the solution. Evaporation and lyophilization from H_2O/CH_3CN gave 0.0114 g

(98%) of compound PM031 (2HCl salt) as a colorless solid. The following characteristic values were obtained by nuclear magnetic resonance spectroscopy:

^1H NMR (CD_3OD) δ: 7.69 s, 7.34 - 7.65 m, 6.20 dt, (J = 7.3, 14.6 Hz), 5.66 dd (J = 8.0, 15.4 Hz), 4.33 m, 3.96 t (J = 6.3 Hz), 3.87 q (J = 6.9 Hz), 3.64 s, 3.57 d (J = 6.7 Hz), 2.86 dd (J = 6.3, 14.1 Hz), 2.78 dd (J = 6.4, 14.1 Hz), 2.41 - 2.51 m, 2.05 q (J = 6.9 Hz), and 1.99 s.

Example 146

Compound PM032

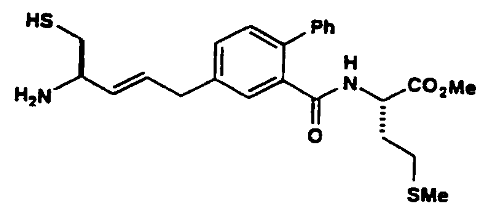


Compound PM032 was prepared in the same manner as that described in Scheme VIII, but 3-thiopheneboronic acid was used in place of benzeneboronic acid in step 3, and L-methionine sulfone methyl ester hydrochloride was used in step 11 in place of L-methionine PNB ester hydrochloride, and the subsequent $Na_2S{\bullet}9H_2O$ step was omitted. Furthermore, between steps 6 and 7 in Scheme VIII, a diimide hydrogenation step was inserted (see Equation 2).

^1H NMR (CD_3OD) δ: 7.34 - 7.48 m, 7.20 dd (J = 1.4, 4.9 Hz), 4.58 dd (J = 4.8, 9.4, 1H), 3.74 s, 2.93 s, 2.86 - 2.99 m, 2.68 - 2.81 m, 2.25 - 2.34 m, 1.98 - 2.14 m, and 1.68 - 1.76 m.

Example 147

Compound PM041

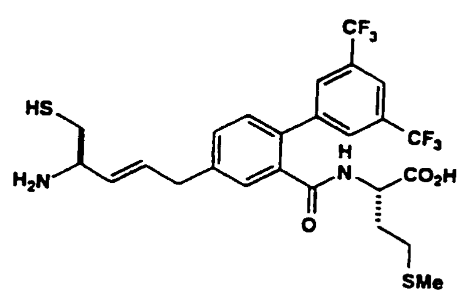


Compound **PM041** was prepared in the same manner as that described in Scheme VIII, but **R017M** was combined with L-methionine methyl ester hydrochloride instead of L-methionine PNB ester hydrochloride, and the subsequent $Na_2S\cdot9H_2O$ step was omitted. The following characteristic values were obtained by nuclear magnetic resonance spectroscopy:

^1H NMR (CD_3OD) δ: 8.40 d, (J = 7.7 Hz), 7.32 - 7.42 m, 6.14 dt (J = 7.2, 14.5 Hz), 5.57 dd (J = 8.1, 15.4 Hz), 4.47 - 4.53 m, 3.87 app q (J = 6.9 Hz), 3.69 s, 3.56 d (J = 6.6 Hz), 2.86 dd (J = 6.2, 14.2 Hz, 2.77 dd (J = 6.4, 14.2 Hz), 2.05 - 2.15 m, 1.88 - 2.00 m, 1.98 s, and 1.68 - 180 m.

Example 148

Compound PM042



Compound **PM042** was prepared in the same manner as that described in Scheme VIII but 3,5-bis(trifluoromethyl)-benzeneboronic acid was used in place of benzeneboronic acid in step 3, and L-methionine *t*-butyl ester hydrochloride was

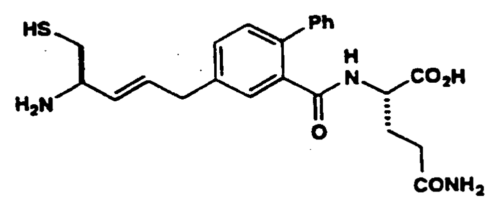
used in step 11 in place of L-methionine PNB ester hydrochloride, and the subsequent $Na_2S \cdot 9H_2O$ step was omitted.

^1H NMR (CD_3OD) δ: 8.59 d (J = 7.5 Hz), 7.93 s, 7.42 - 7.48 m, 6.14 dt (J = 7.2, 14.4 Hz, 5.58 dd (J = 8.0, 15.4 Hz), 4.47 - 4.51 m, 3.87 q (J = 6.9 Hz), 3.59 d (J = 6.6 Hz), 2.85 dd (J = 6.1, 14.0 Hz), 2.77 dd (J = 6.3, 14.2 Hz), 2.06 - 2.24 m, 1.99 s, 1.95 - 2.05 m, and 1.76 - 1.86 m.

$^{19}F\{^1H\}$ NMR ($CDCl_3$, $CFCl_3$ = 0.0 ppm) δ: -62.5 (s).

Example 149

Compound PM051

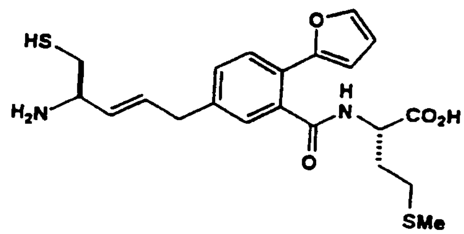


Compound **PM051** was prepared in the same manner as that described in Scheme VIII, but **R017M** was combined with L-glutamine t-butyl ester hydrochloride instead of L-methionine PNB ester hydrochloride, and the subsequent $Na_2S \cdot 9H_2O$ step was omitted. The following characteristic values were obtained by nuclear magnetic resonance spectroscopy:

^1H NMR (CD_3OD) δ: 7.30-7.43 m, 6.13 dt (J = 7.2, 14.4 Hz), 5.57 dd (J = 8.1, 15.4 Hz), 4.32 - 4.35 m, 3.86 app q (J = 6.8 Hz), 3.55 d (J = 6.6 Hz), 2.85 dd (J = 6.3, 14.1 Hz), 2.77 dd (J = 6.3, 14.2 Hz), and 1.77 - 2.06 m.

Example 150

Compound PM052

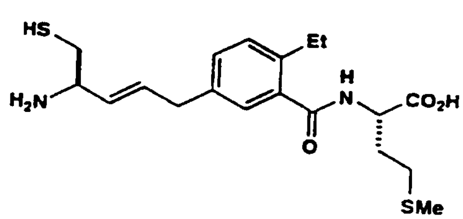


Compound PM052 was prepared in the same manner as that described in Scheme VIII, but 2-furanboronic acid was used in place of benzeneboronic acid in step 3, and L-methionine *t*-butyl ester hydrochloride was used in step 11 in place of L-methionine PNB ester hydrochloride, and the subsequent $Na_2S{\bullet}9H_2O$ step was omitted. 2-Furanboronic acid was obtained according to Thompson et al., *J. Org. Chem.*, 49:5237-5243 (1984).

^1H NMR (CD_3OD) δ: 8.72 d (J = 7.7 Hz), 7.68 d (J = 8.0 Hz), 7.55 d (J = 1.5 Hz), 7.29 - 7.37 m, 6.73 d (J = 3.3 Hz), 6.48 dd (J = 1.8, 3.3 Hz), 6.11 dt (J = 7.1, 14.2 Hz), 5.54 dd (J = 8.2, 15.4 Hz), 4.72 - 4.75 m, 3.85 q (J = 6.8 Hz), 3.52 d (J = 6.5 Hz), 2.85 dd (J = 6.2, 14.2 Hz), 2.75 dd (J = 6.5, 14.3 Hz), 2.41 - 2.63 m, 2.16 - 2.21 m, 2.09 s, and 1.94 - 2.08 m.

Example 151

Compound PM062

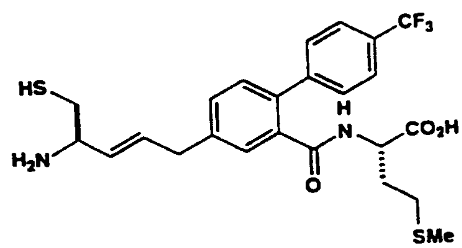


Compound **PM062** was prepared in the same manner as that described for compound **PM212** in Example 175, but step 12, Scheme VIII ($Na_2S \bullet 9H_2O$, omitted in the preparation of **PM212**), was replaced by a $LiOH/MeOH/H_2O$ hydrolysis.

^1H NMR (CD_3OD) δ: 7.26 - 7.33 m, 6.12 dt (J = 7.1, 14.2 Hz), 5.53 dd (J = 8.1, 15.4 Hz), 4.74 - 4.76 m, 3.86 q (J = 6.7 Hz), 3.50 d (J = 6.5 Hz), 2.57 - 2.98 m, 2.21 - 2.30 m, 2.14 s, 2.01 - 2.14 m, and 1.22 t (J = 7.6 Hz).

Example 152

Compound PM071



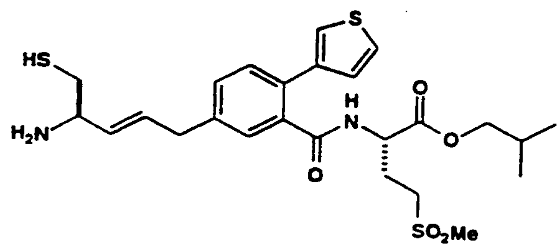
Compound **PM071** was prepared in the same manner as that described in Scheme VIII, but 4-trifluoromethylbenzeneboronic acid was used in place of benzeneboronic acid in step 3, and L-methionine *t*-butyl ester hydrochloride was used in step 11 in place of L-methionine PNB ester hydrochloride, and the subsequent $Na_2S \bullet 9H_2O$ step was omitted. The following characteristic values were obtained by nuclear magnetic resonance spectroscopy:

^1H NMR (CD_3OD) δ: 7.58 - 7.68 m, 7.38 - 7.45 m, 6.14 dt (J = 7.1, 14.2 Hz), 5.57 dd (J = 7.7, 15.0 Hz), 4.50 - 4.52 m, 3.82 - 3.90 m, 3.57 d (J = 6.4 Hz), 2.85 dd (J = 5.9, 13.9 Hz), 2.76 dd (J = 6.1, 14.1 Hz), 2.18 - 2.30 m, 1.94 - 2.12 m, 2.00 s, and 1.78 - 1.86 m.

$^{19}F\{^1H\}$NMR ($CDCl_3$, $CFCl_3$ = 0.0 ppm) δ: -62.3 s.

Example 153

Compound PM072

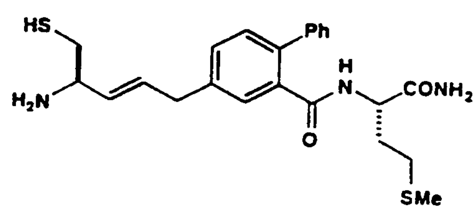


Compound PM072 was prepared in the same manner as that described in Scheme VIII, but 3-thiopheneboronic acid was used in place of benzeneboronic acid in step 3, and L-methioninesulfone isobutyl ester hydrochloride was used in step 11 in place of L-methionine PNB ester hydrochloride, and the subsequent $Na_2S \bullet 9H_2O$ step was omitted.

^1H NMR (CD_3OD) δ: 8.65 d (J = 7.8 Hz), 7.36 - 7.56 m, 7.24 d (J = 1.3, 4.9 Hz), 6.15 dt (J = 7.2, 14.5 Hz), 5.59 dd (J = 8.0, 15.4 Hz), 4.58 - 4.63 m, 3.98 d (J = 6.6 Hz), 3.89 q (J = 6.9 Hz), 3.57 d (J = 6.5 Hz), 2.95 s, 2.70 - 3.00 m, 2.29 - 2.37 m, 1.96 - 2.10 m, and 0.99 d (J = 6.7 Hz).

Example 154

Compound PM081



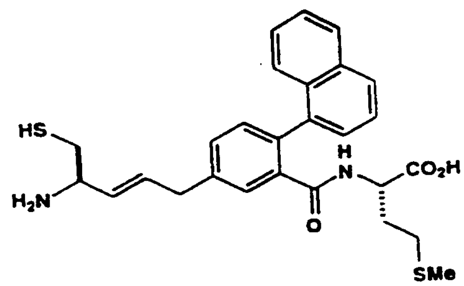
Therapeutic compound PM081 was prepared in the same manner as that described in Scheme VIII, but L-methionine amide hydrochloride was used in step 11 in place of L-methionine PNB ester hydrochloride, and the subsequent $Na_2S \bullet 9H_2O$ step was omitted. The following characteristic

values were obtained by nuclear magnetic resonance spectroscopy:

^{1}H NMR (CD_3OD) δ: 7.34 - 7.44 m, 6.16 dt (J = 7.2, 14.3 Hz), 5.60 dd (J = 8.0, 15.4 Hz), 4.40 - 4.44 m, 3.89 q (J = 6.8 Hz), 3.58 d (J = 7.0 Hz), 2.88 dd (J = 6.3, 14.2 Hz), 2.79 dd (J = 6.4, 14.2 Hz), 2.00 - 2.14 m, 2.03 s, 1.85 - 1.94 m, and 1.66 - 1.75 m.

Example 155

Compound **PM082**

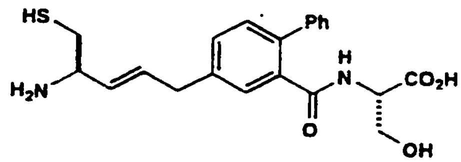


Compound **PM082** was prepared in the same manner as that described in Scheme VIII, but 1-naphthaleneboronic acid was used in place of benzeneboronic acid in step 3, and L-methionine *t*-butyl ester hydrochloride was used in step 11 in place of L-methionine PNB ester hydrochloride, and the subsequent $Na_2S \cdot 9H_2O$ step was omitted. (Note: this compound exhibits rotational isomerism in the ^{1}H NMR at room temp.)

^{1}H NMR (CD_3OD) δ: 7.85 - 7.92 m, 7.19 - 7.64 m, 6.19 dt (J = 7.2, 14.5 Hz), 5.60 - 5.67 m, 4.24 dd (J = 3.6, 8.9 Hz), 4.18 dd (J = 4.1, 8.7 Hz), 3.87 - 3.91 m, 3.62 d (J = 6.6 Hz), 2.88 dd (J = 6.3, 13.8 Hz), 2.79 dd (J = 6.3, 14.1 Hz), 1.81 s, 1.76 s, and 1.19 - 1.81 m.

Example 156

Compound PM091

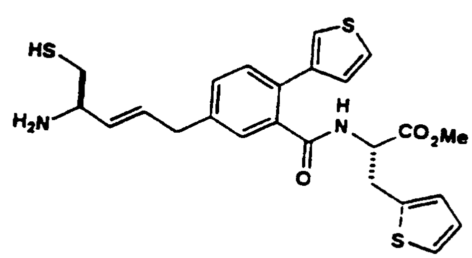


Compound RM091 was prepared in the same manner as that described in Scheme VIII, but R017M was combined with L-serine *t*-butyl ester *t*-butyl ether hydrochloride instead of L-methionine PNB ester hydrochloride, and the subsequent $Na_2S{\bullet}9H_2O$ step was omitted. The following characteristic values were obtained by nuclear magnetic resonance spectroscopy:

^{1}H NMR (CD_3OD) δ: 7.33 - 7.60 m, 6.18 dt (J = 7.2, 14.5 Hz), 5.56 dd (J = 8.0, 15.4 Hz), 4.49 - 4.51 m, 3.90 app q (J = 6.9 Hz), 3.84 dd (J = 4.8, 11.1 Hz), 3.67 dd (J = 4.1, 11.1 Hz), 3.59 d (J = 6.5 Hz), 2.89 dd (J = 6.1, 14.2 Hz), and 2.79 dd (J = 6.4, 14.2 Hz).

Example 157

Compound PM092



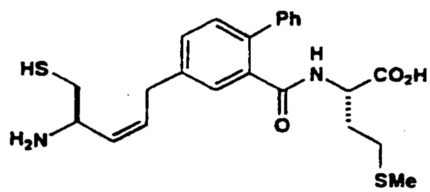
Compound PM092 was prepared in the same manner as that described in Scheme VIII, but 3-thiopheneboronic acid was used in place of benzeneboronic acid in step 3, L-3-(2-thienyl)-alanine methyl ester hydrochloride was used in step 11 in

place of L-methionine PNB ester hydrochloride, and the subsequent $Na_2S \cdot 9H_2O$ step was omitted.

^1H NMR (CD_3OD) δ: 7.30 - 7.47 m, 7.24 m, 7.13 dd (J = 1.2, 4.9 Hz), 6.97 dd (J = 3.5, 5.1 Hz), 6.83 m, 6.14 dt (J = 7.2, 14.5 Hz), 5.56 dd (J = 7.7, 15.4 Hz), 4.79-4.82 m, 3.88 q (J = 6.7 Hz), 3.76 s, 3.54 d (J = 6.2 Hz), 3.19-3.42 m, 2.88 dd (J = 6.1, 14.1 Hz), and 2.78 dd (J = 6.3, 14.2 Hz).

Example 158

Compound PM101

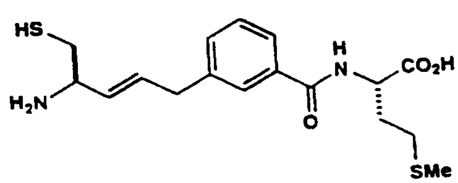


Compound **PM101** was prepared according to Scheme VIII with the substitution of **R013M cis** for **R013M trans**. The following characteristic values were obtained by nuclear magnetic resonance spectroscopy:

^1H NMR (CD_3OD) δ: 7.30 - 7.44 m, 6.08 dt (J = 5.3, 15.3 Hz), 5.50 app tt (J = 1.3, 10.3 Hz), 4.45 - 4.49 m, 4.35 dt (J = 4.5, 13.0 Hz), 3.64 app d (J = 7.5 Hz), 2.74 - 2.86 m, 2.04 - 2.12 m, 1.92 - 2.00 m, 1.99 s, and 1.68 - 1.80 m.

Example 159

Compound PM102

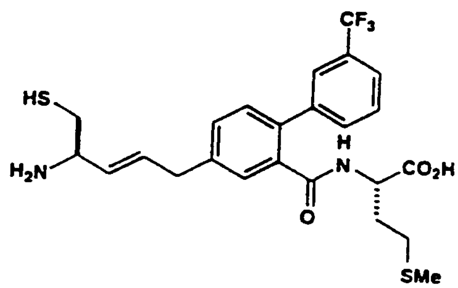


Compound **PM102** was prepared in the same manner as that described in Scheme VIII, but 3-carboxybenzaldehyde was used in place of 5-formylsalicylic acid in step 1, steps 2 and 3 were omitted, L-methionine *t*-butyl ester hydrochloride was used in step 11 in place of L-methionine PNB ester hydrochloride, and the subsequent $Na_2S \bullet 9H_2O$ step was omitted.

^1H NMR (CD_3OD) δ: 7.73 - 7.76 m, 7.44 - 7.47 m, 6.15 dt (J = 7.3, 14.6 Hz), 5.57 dd (J = 8.0, 15.4 Hz), 4.80 br dd (J = 4.6, 9.5 Hz), 3.89 q (J = 6.8 Hz, 1H), 3.57 d (J = 6.7 Hz), 2.88 dd (J = 6.1, 14.2 Hz), 2.79 dd (J = 6.3, 14.1 Hz), 2.53 - 2.74 m, 2.22 - 2.33 m, 2.13 s, and 2.03 - 2.20 m.

Example 160

Compound PM111



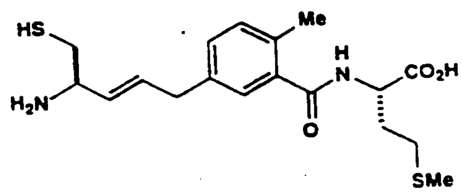
Compound **PM111** was prepared in the same manner as that described in Scheme VIII, but 3-trifluoromethylbenzeneboronic acid was used in place of benzeneboronic acid in step 3, and L-methionine methyl ester hydrochloride was used in step 11 in place of L-methionine PNB ester hydrochloride, and the subsequent $Na_2S \bullet 9H_2O$ step was replaced with a LiOH/MeOH/H_2O hydrolysis. The following characteristic values were obtained by nuclear magnetic resonance spectroscopy:

^1H NMR (CD_3OD) δ: 7.57 - 7.68 m, 7.39 - 7.45 m, 6.14 dt (J = 7.7, 15.3 Hz), 5.58 dd (J = 8.0, 15.4 Hz), 4.46 - 4.48 m, 3.87 q (J = 7.4 Hz), 3.58 d (J = 6.5 Hz), 2.86 dd (J = 6.2,

14.2 Hz), 2.77 dd (J = 6.4, 14.2 Hz), 1.92 - 2.18 m, 1.99 s, and 1.72 - 1.82 m.

Example 161

Compound PM112

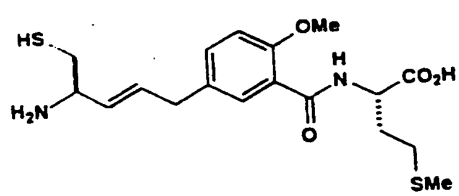


Compound **PM112** was prepared in the same manner as that described in Scheme VIII, but tetramethyltin (with LiCl in DMF) was used in place of benzeneboronic acid in step 3, and L-methionine t-butyl ester hydrochloride was used in step 11 in place of L-methionine PNB ester hydrochloride, and the subsequent $Na_2S{\bullet}9H_2O$ step was omitted.

^1H NMR (CD_3OD) δ: 8.58 d (J = 7.7 Hz), 7.18 - 7.28 m, 6.09 dt (J = 7.2, 14.4 Hz), 5.50 dd (J = 8.0, 15.4 Hz), 4.73 br dd (J = 4.5, 9.6 Hz), 3.84 q (J = 6.8 Hz), 3.47 d, (J = 6.4 Hz), 2.83 dd (J = 6.2, 14.2 Hz), 2.74 dd (J = 6.4, 14.1 Hz), 2.48 - 2.69 m, 2.38 s, 2.18 - 2.28 m, 2.11 s, and 1.99 - 2.10 m.

Example 162

Compound PM122



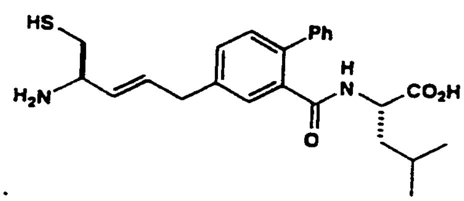
Compound **PM122** was prepared in the same manner as that described in Scheme VIII, but step 2 was replaced with a dimethyl sulfate alkylation step, step 3 was omitted,

L-methionine *t*-butyl ester hydrochloride was used in step 11 in place of L-methionine PNB ester hydrochloride, and the subsequent $Na_2S{\bullet}9H_2O$ step was omitted.

^1H NMR (CD_3OD) δ: 7.80 d (J = 2.2 Hz), 7.41 dd (J = 2.1, 8.4 Hz), 7.15 d (J = 8.4 Hz), 6.12 dt (J = 7.2, 14.4 Hz), 5.53 dd (J = 8.0, 15.4 Hz), 4.81 dd (J = 4.9, 7.6 Hz), 4.01 s, 3.85 - 3.96 m, 3.48 d (J = 6.6 Hz), 2.87 dd (J = 6.1, 14.1 Hz), 2.77 dd (J = 6.4, 14.1 Hz), 2.58 - 2.63 m, 2.25 - 2.32 m, 2.12 s, and 2.10 - 2.20 m.

Example 163

Compound **PM131**

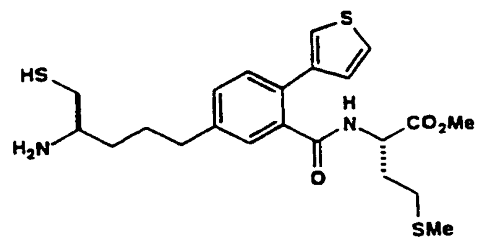


Compound **PM131** was prepared in the same manner as that described in Scheme VIII, but **R017M** was combined with L-leucine PNB ester hydrochloride instead of L-methionine PNB ester hydrochloride, and the remaining steps were as described in Scheme VIII. The following characteristic values were obtained by nuclear magnetic resonance spectroscopy:

^1H NMR (CD_3OD) δ: 8.25 d (J = 7.7 Hz), 7.31 - 7.41 m, 6.14 dt (J = 7.0, 15.2 Hz), 5.57 dd (J = 8.0, 15.4 Hz), 4.31 - 4.35 m, 4.15 q (J = 7.1 Hz), 3.85 app q (J = 5.3 Hz), 3.55 d (J = 6.6 Hz), 2.86 dd (J = 6.2, 14.2 Hz), 2.76 dd (J = 6.4, 14.2 Hz), 1.28 - 1.46 m, 1.05 - 1.12 m, 0.79 d (J = 6.6 Hz), and 0.76 d (J = 6.5 Hz).

Example 164

Compound PM132

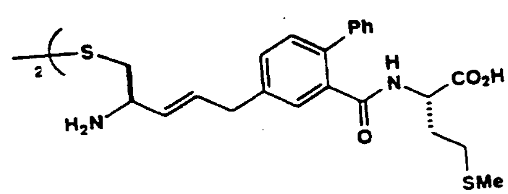


Compound **PM132** was prepared in the same manner as that described in Scheme VIII, but 3-thiopheneboronic acid was used in place of benzeneboronic acid in step 3, L-methionine methyl ester hydrochloride was used in step 11 in place of L-methionine PNB ester hydrochloride, and the subsequent $Na_2S{\bullet}9H_2O$ step was omitted. Furthermore, between steps 6 and 7 in Scheme VIII, a diimide hydrogenation step was inserted (see Equation 2).

^1H NMR (CD_3OD) δ: 7.25 - 7.45 m, 7.19 dd (J = 1.6, 4.8 Hz), 4.59 dd (J = 4.4, 9.6, 1H), 2.89 dd (J = 4.6, 14.7 Hz), 2.72 - 2.75 m, 2.71 dd (J = 6.4, 14.7 Hz), 2.25 - 2.32 m, 2.14 - 2.22 m, 2.03 s, 1.97 - 2.06 m, and 1.69 - 1.87 m.

Example 165

Compound PM141



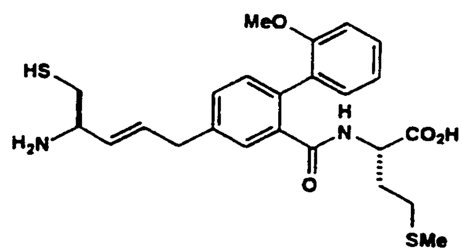
Compound **PM041** hydrochloride (0.0320 g, 0.06464 mmol) was dissolved in MeOH (16 mL) and H_2O (6 mL), and LiOH (0.0312 g, 1.3027 mmol) was added. The resulting solution was stirred

for 24 h at room temp, quenched with TFA (0.110 mL), and evaporated. The residue was purified by RP HPLC to give 0.0276 g (78%) of therapeutic compound **PM141** (2 TFA salt). The following characteristic values were obtained by nuclear magnetic resonance spectroscopy:

^1H NMR (CD_3OD) δ: 7.31 - 7.41 m, 6.09 dt (J = 7.2, 14.4 Hz), 5.55 dd (J = 8.3, 15.4 Hz), 4.46 - 4.49 m, 4.06 q (J = 7.3 Hz), 3.50 d (J = 6.7 Hz), 3.06 d (J = 7.2 Hz), 2.07 - 2.15 m, 1.92 - 2.00 m, 1.98 s, and 1.71 - 1.79 m.

Example 166

<u>Compound **PM142**</u>



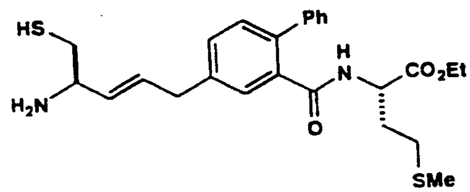
Compound **PM142** was prepared in the same manner as that described in Scheme VIII, but 2-methoxybenzeneboronic acid was used in place of benzeneboronic acid in step 3, and L-methionine *t*-butyl ester hydrochloride was used in step 11 in place of L-methionine PNB ester hydrochloride, and the subsequent $Na_2S{\bullet}9H_2O$ step was omitted. 2-Methoxybenzene-boronic acid was obtained according to Thompson et al., *J. Org. Chem.*, 49:5237-5243 (1984), and Eggers et al., *Inorg. Chem.*, 6:160-161 (1967).

^1H NMR (CD_3OD) δ: 7.44 - 7.48 m, 7.32 - 7.39 m, 7.20 - 7.24 m, 6.08 - 7.03 m, 6.14 dt (J = 7.2, 14.4 Hz), 5.58 dd (J = 8.1, 15.4 Hz), 4.43 - 4.47 m, 3.87 q (J = 6.6 Hz), 3.74 s, 3.55 d (J = 6.4 Hz), 2.86 dd (J = 6.1, 14.2 Hz), 2.76 dd

(J = 6.4, 14.0 Hz), 1.99 s, 1.98 - 2.16 m, 1.89 - 1.94 m, and 1.65 - 1.70 m.

Example 167

Compound PM151

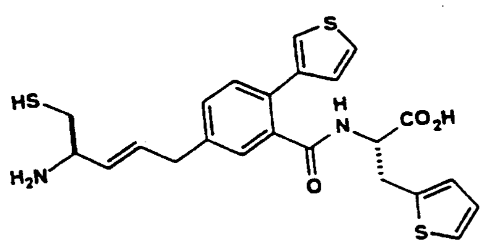


Compound **PM041** was prepared in the same manner as that described in Scheme VIII, but **R017M** was combined with L-methionine ethyl ester hydrochloride instead of L-methionine PNB ester hydrochloride, and the subsequent $Na_2S \cdot 9H_2O$ step was omitted. The following characteristic values were obtained by nuclear magnetic resonance spectroscopy:

^{1}H NMR (CD_3OD) δ: 8.39 d (J = 7.7 Hz), 7.31 - 7.41 m, 6.13 dt (J = 7.2, 15.2 Hz), 5.57 dd (J = 8.0, 15.4 Hz), 4.45 - 4.50 m, 4.15 q, (J = 7.1 Hz), 3.86 app q, (J = 6.8 Hz), 3.55 d (J = 6.7 Hz), 2.85 dd (J = 6.3, 14.1 Hz), 2.77 dd (J = 6.3, 14.1 Hz), 2.05 - 2.15 m, 1.88 - 2.00 m, 1.98 s, 1.69 - 1.81 m, and 1.25 t (J = 7.1 Hz).

Example 168

Compound PM152



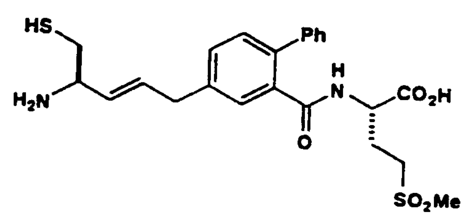
Compound **PM152** was prepared in the same manner as that described in Scheme VIII, but 3-thiopheneboronic acid was used

in place of benzeneboronic acid in step 3, L-3-(2-thienyl)-alanine methyl ester hydrochloride was used in step 11 in place of L-methionine PNB ester hydrochloride, and the subsequent $Na_2S\bullet9H_2O$ step was replaced by a $LiOH/MeOH/H_2O$ hydrolysis.

^1H NMR (CD_3OD) δ: 7.25 - 7.46 m, 7.12 dd (J = 1.8, 4.5 Hz), 6.97 dd, (J = 3.5, 5.1 Hz), 6.86 d (J = 2.7 Hz), 6.15 dt (J = 7.2, 14.4 Hz), 5.56 dd (J = 7.9, 15.4 Hz), 4.79 dd (J = 4.6, 9.2 Hz), 3.89 q (J = 6.8 Hz), 3.53 d (J = 6.5 Hz), 3.45 dd (J = 4.7, 15.0 Hz), 3.25 dd (J = 9.2, 14.9 Hz), 2.88 dd (J = 6.1, 14.2 Hz), and 2.79 dd (J = 6.4, 14.1 Hz).

Example 169

Compound PM161

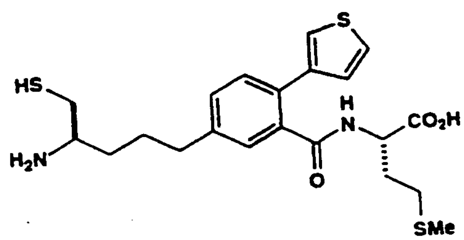


Compound **PM161** was prepared in the same manner as that described in Scheme VIII, but **R017M** was combined with L-methioninesulfone methyl ester hydrochloride in step 11 in place of L-methionine PNB ester hydrochloride, and the subsequent $Na_2S\bullet9H_2O$ step was replaced with a $LiOH/MeOH/H_2O$ hydrolysis. The following characteristic values were obtained by nuclear magnetic resonance spectroscopy:

^1H NMR (CD_3OD) δ: 7.37 - 7.46 m, 6.16 dt (J = 7.2, 14.4 Hz), 5.61 dd (J = 8.1, 15.4 Hz), 4.49 br dd (J = 4.5, 9.5 Hz), 3.89 q (J = 6.8 Hz), 3.58 d (J = 6.7 Hz), 2.90 s, 2.74 - 2.90 m, 2.52 - 2.59 m, 2.23 - 2.32 m, and 1.95 - 2.03 m.

Example 170

Compound PM162

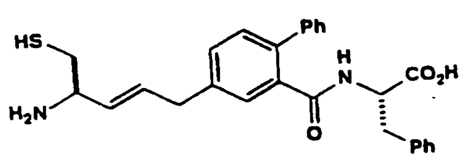


Compound PM162 was prepared in the same manner as that described in Scheme VIII, but 3-thiopheneboronic acid was used in place of benzeneboronic acid in step 3, and L-methionine t-butyl ester hydrochloride was used in step 11 in place of L-methionine PNB ester hydrochloride, and the subsequent $Na_2S{\bullet}9H_2O$ step was omitted. Furthermore, between steps 6 and 7 in Scheme VIII, a diimide hydrogenation step was inserted (see Equation 2).

^1H NMR (CD_3OD) δ: 8.47 d (J = 7.7 Hz), 7.37 - 7.47 m, 7.23 dd (J = 1.9, 4.3 Hz), 4.57 - 4.62 m, 2.91 dd (J = 4.5, 14.7 Hz), 2.71 - 2.86 m, 2.28 - 2.35 m, 2.17 - 2.25 m, 2.06 s, 2.04 - 2.12 m, and 1.70 - 1.91 m.

Example 171

Compound PM172



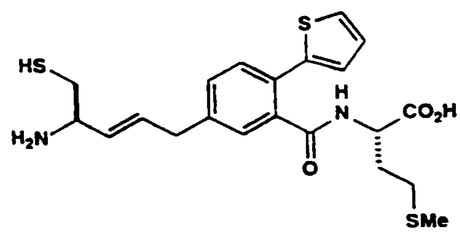
Compound PM172 was prepared in the same manner as that described in Scheme VIII, but L-phenylalanine *t*-butyl ester hydrochloride was used in step 11 in place of L-methionine PNB

ester hydrochloride, and the subsequent $Na_2S{\bullet}9H_2O$ step was omitted.

^1H NMR (CD_3OD) δ: 8.41 d (J = 7.9 Hz), 7.17 - 7.48 m, 6.14 dt (J = 7.1, 14.2 Hz), 5.58 dd (J = 8.0, 15.4 Hz), 4.72 br dd (J = 5.1, 9.4 Hz), 3.88 q (J = 6.8 Hz, 1H), 3.54 d (J = 6.5 Hz), 3.17 dd (J = 5.0, 13.9 Hz), 2.86 - 2.95 m, and 2.79 dd (J = 6.4, 14.2 Hz).

Example 172

Compound PM182

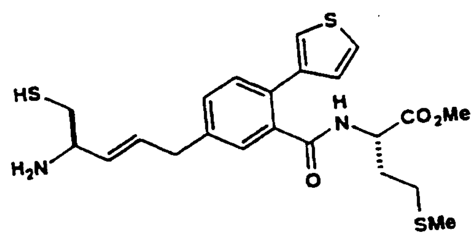


Compound PM182 was prepared in the same manner as that described in Scheme VIII, but 2-thiopheneboronic acid was used in place of benzeneboronic acid in step 3, and L-methionine t-butyl ester hydrochloride was used in step 11 in place of L-methionine PNB ester hydrochloride, and the subsequent $Na_2S{\bullet}9H_2O$ step was omitted.

^1H NMR (CD_3OD) δ: 7.30 - 7.50 m, 7.21 d (J = 2.6 Hz), 7.08 d (J = 3.6, 5.0 Hz), 6.15 dt (J = 7.2, 14.3 Hz), 5.58 dd (J = 8.0, 15.4 Hz), 4.61 br m, 3.89 q (J = 6.9 Hz), 3.56 d (J = 6.4 Hz), 2.88 dd (J = 6.2, 14.2 Hz), 2.79 dd (J = 6.4, 14.2 Hz), 2.29 - 2.36 m, 2.17 - 2.25 m, 2.06 s, 2.05 - 2.14 m, and 1.79 - 1.90 m.

Example 173

Compound PM192

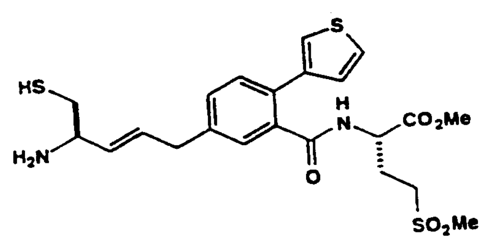


Compound **PM192** was prepared in the same manner as that described in Scheme VIII, but 3-thiopheneboronic acid was used in place of benzeneboronic acid in step 3, and L-methionine methyl ester hydrochloride was used in step 11 in place of L-methionine PNB ester hydrochloride, and the subsequent $Na_2S \cdot 9H_2O$ step was omitted.

^1H NMR (CD_3OD) δ: 7.33 - 7.48 m, 7.22 dd (J = 2.0, 4.4 Hz) 6.16 dt (J = 7.2, 15.4 Hz), 5.59 dd (J = 8.1, 15.4 Hz), 4.59 - 4.65 m, 3.89 q (J = 6.9 Hz), 3.75 s, 3.57 d, (J = 6.3 Hz), 2.88 dd (J = 6.7, 13.8 Hz), 2.80 dd (J = 6.3, 14.1 Hz), 2.28-2.35 m, 2.18-2.25 m, 2.06 s, 2.00 - 2.11 m, and 1.81 - 1.90 m.

Example 174

Compound PM202



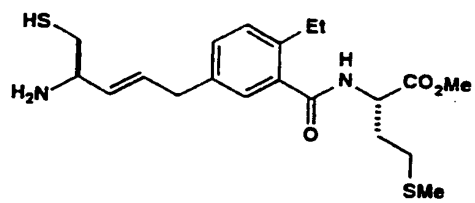
Compound **PM202** was prepared in the same manner as that described in Scheme VIII, but 3-thiopheneboronic acid was used in place of benzeneboronic acid in step 3, and L-methioninesulfone methyl ester hydrochloride was used in

step 11 in place of L-methionine PNB ester hydrochloride, and the subsequent $Na_2S \cdot 9H_2O$ step was omitted.

^1H NMR (CD_3OD) δ: 7.35 - 7.50 m, 7.23 dd (J = 1.1, 4.8 Hz), 6.15 dt (J = 7.2, 14.3 Hz), 5.59 dd (J = 8.0, 15.4 Hz), 4.61 br dd (J = 4.7, 9.4 Hz), 3.89 br q (J = 6.6, 13.6 Hz), 3.77 s, 3.56 d (J = 6.5 Hz) 2.95 s, 2.76 - 3.01 m, 2.28 - 2.37 m, and 2.01 - 2.11 m.

Example 175

Compound PM212



Compound **PM212** was prepared in the same manner as that described in Scheme VIII, but tetravinyltin (with LiCl in DMF) was used in place of benzeneboronic acid in step 3, followed by a catalytic hydrogenation step (see Equation 1), and L-methionine methyl ester hydrochloride was used in step 11 in place of L-methionine PNB ester hydrochloride, and the subsequent $Na_2S \cdot 9H_2O$ step was omitted.

^1H NMR (CD_3OD) δ: 8.76 d (J = 7.5 Hz), 7.24 - 7.36 m, 6.13 dt (J = 7.1, 14.3 Hz), 5.54 dd (J = 8.1, 15.4 Hz), 4.76 - 4.81 m, 3.87 q (J = 6.8 Hz), 3.79 s, 3.50 d (J = 6.3 Hz), 2.56 - 2.89 m, 2.18 - 2.26 m, 2.13 s, 2.01 - 2.13 m, and 1.22 t (J = 7.6 Hz).

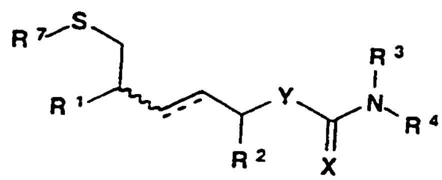
OTHER EMBODIMENTS

From the above description, one skilled in the art can easily ascertain the essential characteristics of the present invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions. Thus, other embodiments are also withing the claims.

What is claimed is:

CLAIMS

1. A compound having the formula:



(I)

wherein R^1 is H, NHR^8, or NR^8R^9, wherein R^8 is H, C_{1-6} alkyl, C_{1-6} acyl, C_{2-14} alkyloxycarbonyl or any other amino-protecting group, and R^9 is C_{1-6} alkyl, C_{1-6} acyl, or C_{2-14} alkyloxycarbonyl; or, when taken together with R^7, a bifunctional organic moiety of fewer than 50 carbon atoms;

R^2 is H, C_{1-8} alkyl, (C_{6-40} aryl)(C_{0-6} alkyl), or (C_{3-10} heteroaryl)(C_{0-6} alkyl);

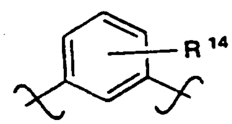
R^3 is H, C_{1-6} alkyl, or (C_{6-40} aryl)(C_{0-6} alkyl);

R^4 is C_{3-16} cycloalkyl, (C_{3-16} heterocyclic radical)-(C_{0-6} alkyl), (C_{6-12} aryl)(C_{0-6} alkyl), (C_{3-16} heteroaryl)-(C_{0-6} alkyl), R^5(CH-)(C=O)R^6, R^5(CH-)(C=S)R^6, R^5(CH-)(CH_2)R^6, R^5(CH_2-), or any other amino-protecting group, wherein R^5 is C_{1-6} alkyl, (C_{3-10} heterocyclic radical)(C_{0-6} alkyl), (C_{3-10} heteroaryl)(C_{1-6} alkyl), hydroxymethyl, $-(CH_2)_n$-A-$(CH_2)_m$-CH_3, $-(CH_2)_n(C{=}O)NH_2$, or $-(CH_2)_n(C{=}O)NH(CH_2)_mCH_3$ (wherein A is O, S, SO, or SO_2, n is 0, 1, 2 or 3, and m is 0, 1, or 2), or any other side chain of a naturally occurring amino acid; and R^6 is H, NH_2, NHOH, C_{3-16} heterocyclic radical, C_{3-16} heteroaryl, NHR^{10}, $NR^{10}R^{11}$, OR^{12}, $NR^{10}OR^{11}$, or $NHOR^{13}$, or any other carboxyl-protecting group, wherein each of R^{10} and R^{11}, independently, is C_{1-6} alkyl, (C_{3-16} heterocyclic radical)(C_{0-6} alkyl), C_{2-14} acyloxycarbonyl, (C_{3-16} heteroaryl)-(C_{0-6} alkyl), or any other amino-protecting group, R^{12} is H, C_{1-6} alkyl, (C_{1-12} acyl)oxy(C_{1-12} alkyl), (C_{1-12} alkyl)oxy-

$(C_{1-12}$ alkyl), or C_{2-14} alkyloxycarbonyl, or any other hydroxyl- or carboxyl-protecting group, and R^{13} is H, C_{1-6} alkyl, or $(C_{6-40}$ aryl)$(C_{0-6}$ alkyl);

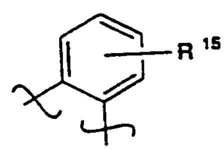
X is =O, =S, or two singly-bonded H;

Y is selected from the following five formulae:



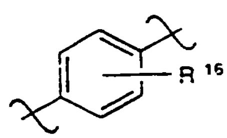
(i)

wherein R^{14} is H, halide, hydroxy, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-12} alkoxy, C_{1-6} acyloxy, C_{1-6} acyl, C_{6-41} aryl, C_{3-40} heterocyclic radical, C_{3-40} heteroaryl, C_{1-12} alkylsulfonyloxy, C_{1-12} haloalkylsulfonyloxy, C_{6-40} arylsulfonyloxy, or C_{6-41} aryloxy;



(ii)

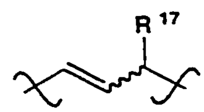
wherein R^{15} is H, halide, hydroxy, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-12} alkoxy, C_{1-6} acyloxy, C_{1-6} acyl, C_{6-41} aryl, C_{3-40} heterocyclic radical, C_{3-40} heteroaryl, C_{1-12} alkylsulfonyloxy, C_{1-12} haloalkylsulfonyloxy, C_{6-40} arylsulfonyloxy, or C_{6-41} aryloxy;



(iii)

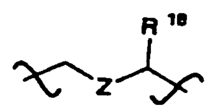
wherein R^{16} is H, halide, hydroxy, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-12} alkoxy, C_{1-6} acyloxy, C_{1-6} acyl, C_{6-41} aryl, C_{3-40} heterocyclic radical, C_{3-40} heteroaryl,

C_{1-12} alkylsulfonyloxy, C_{1-12} haloalkylsulfonyloxy, C_{6-40} arylsulfonyloxy, or C_{6-41} aryloxy;



(iv)

wherein R^{17} is H, C_{1-8} alkyl, (C_{6-40} aryl)(C_{0-6} alkyl), (C_{3-10} heteroaryl)(C_{0-6} alkyl), or (C_{3-10} heterocyclic radical)-(C_{0-6} alkyl); and



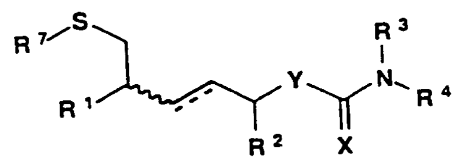
(v)

wherein R^{18} is H, C_{1-8} alkyl, (C_{6-40} aryl)(C_{0-6} alkyl), (C_{3-10} heterocyclic radical)(C_{0-6} alkyl), or (C_{3-10} heteroaryl)-(C_{0-6} alkyl), and Z is O, S, SO, SO_2, or NR^{19} wherein R^{19} is H, C_{1-6} alkyl, C_{1-6} acyl, (C_{6-40} aryl)(C_{0-6} alkyl), C_{3-10} heterocyclic radical, C_{3-10} heteroaryl, (C_{3-10} heteroaryl)(C_{0-6} alkyl), or C_{2-14} alkyloxycarbonyl; or wherein R^{18} and NR^{19} taken together form a bifunctional C_{6-40} aryl, a bifunctional C_{3-12} heterocyclic radical, or a bifunctional C_{3-12} heteroaryl; and

R^7 is an organic moiety having fewer than 50 carbon atoms or, when taken together with R^1, a bifunctional organic moiety having fewer than 50 carbon atoms;

or a pharmaceutically acceptable salt thereof.

2. A compound of claim 1, having the formula:



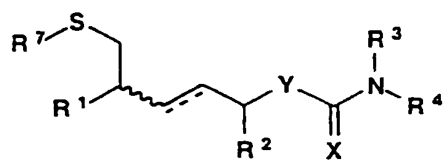
(II)

wherein R^1 is H, NHR^8, or NR^8R^9, wherein R^8 is H, C_{1-6} alkyl, C_{1-6} acyl, C_{2-14} alkyloxycarbonyl or any other amino-protecting group, and R^9 is C_{1-6} alkyl, C_{1-6} acyl, C_{2-14} alkyloxycarbonyl or, when taken together with R^7, a bifunctional thiol-protecting group; and

R^7 is H; a thiol protecting group or, when taken together with R^9, a bifunctional thiol-protecting group; or a moiety set forth in the above generic formula (II) wherein R^7 is deleted, said compound being a symmetrical disulfide dimer or an asymmetrical disulfide;

or a pharmaceutically acceptable salt thereof.

3. A compound of claim 2, having the following formula:



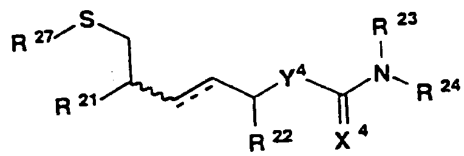
(III)

wherein R^1 is NHR^8 or NR^8R^9, wherein R^8 is C_{1-6} alkyl, C_{1-6} acyl, C_{2-14} alkyloxycarbonyl, or any other amino-protecting group, and R^9 is C_{1-6} alkyl, C_{1-6} acyl, C_{2-14} alkyloxycarbonyl or, when taken together with R^7, a bifunctional thiol-protecting group;

R^6 is H, NH_2, NHOH, C_{3-10} heterocyclic radical, C_{3-10} heteroaryl, NHR^{10}, $NR^{10}R^{11}$, OR^{12}, $NR^{10}OR^{11}$, $NHOR^{13}$, or any other carboxyl-protecting group (wherein each of R^{10} and R^{11}, independently, is C_{1-6} alkyl, (C_{3-16} heterocyclic radical)-(C_{0-6} alkyl), C_{2-14} alkyloxycarbonyl, or (C_{3-16} heteroaryl)-(C_{1-6} alkyl)), R^{12} is C_{1-6} alkyl, (C_{1-12} acyl)oxy(C_{1-12} alkyl), (C_{1-12} alkyl)oxy(C_{1-12} alkyl), or C_{2-14} alkyloxycarbonyl, and R^{13} is H, C_{1-6} alkyl, or (C_{6-40} aryl)(C_{0-6} alkyl);

R^7 is a thiol-protecting group, or, when taken together with R^9, a bifunctional thiol-protecting group; or a moiety set forth in the above generic formula (III) wherein R^7 is deleted, said compound being a symmetrical disulfide dimer or an asymmetrical disulfide.

4. A compound having the following formula:



(IV)

wherein R^{21} is H, NH_2, NHR^{28}, or $NR^{28}R^{29}$, wherein each R^{28} and R^{29}, independently, is C_{1-6} alkyl, C_{1-6} acyl, or C_{2-14} alkyloxycarbonyl;

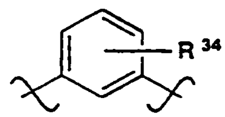
R^{22} is H, C_{1-8} alkyl, (C_{6-40} aryl)(C_{0-6} alkyl), or (C_{3-10} heteroaryl)(C_{0-6} alkyl);

R^{23} is H, C_{1-8} alkyl, or (C_{6-40} aryl)(C_{0-6} alkyl);

R^{24} is C_{3-16} cycloalkyl, (C_{6-12} aryl)(C_{0-6} alkyl), (C_{3-16} heterocyclic radical)(C_{0-6} alkyl), (C_{3-10} heteroaryl)-(C_{0-6} alkyl), R^{25}(CH-)(C=O)R^{26}, R^{25}(CH-)(C=S)R^{26}, R^{25}(CH-)(CH_2)R^{26}, or R^{25}(CH_2-), wherein R^{25} is C_{1-6} alkyl, (C_{6-12} aryl)(C_{0-6} alkyl), (C_{3-10} heterocyclic radical)-(C_{0-6} alkyl), (C_{3-10} heteroaryl)(C_{0-6} alkyl), hydroxymethyl, $-(CH_2)_n-A^4-(CH_2)_m-CH_3$, $-(CH_2)_n(C{=}O)NH_2$, or $-(CH_2)_n(C{=}O)NH-(CH_2)_mCH_3$ (wherein A^4 is O, S, SO, or SO_2, n is 0, 1, 2 or 3, and m is 0, 1, or 2), or any other side chain of a naturally occurring amino acid; and R^{26} is H, NH_2, NHOH, C_{3-16} heterocyclic radical, C_{3-16} heteroaryl, NHR^{30}, $NR^{30}R^{31}$, OR^{32}, $NR^{30}OR^{31}$, or $NHOR^{33}$, wherein each of R^{30} and R^{31}, independently, is C_{1-6} alkyl, (C_{6-12} aryl)(C_{0-6} alkyl), C_{2-14} alkyloxy-carbonyl, (C_{3-16} heterocyclic radical)(C_{0-6} alkyl), or (C_{3-16} heteroaryl)(C_{0-6} alkyl), R^{32} is H, C_{1-6} alkyl, (C_{1-12} acyl)oxy(C_{1-12} alkyl), (C_{1-12} alkyl)oxy-(C_{1-12} alkyl), or C_{2-14} alkyloxycarbonyl, and R^{33} is H, C_{1-6} alkyl, or (C_{6-40} aryl)(C_{0-6} alkyl);

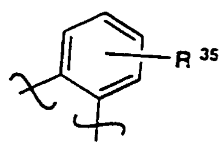
X^4 is =O, =S, or two singly-bonded H;

Y^4 is selected from the following five formulae:



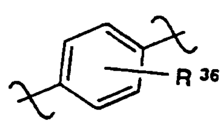
(vi)

wherein R^{34} is H, halide, hydroxy, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-12} alkoxy, C_{1-6} acyloxy, C_{1-6} acyl, C_{6-41} aryl, C_{3-40} heterocyclic radical, C_{3-40} heteroaryl, C_{1-12} alkylsulfonyloxy, C_{1-12} haloalkylsulfonyloxy, C_{6-40} arylsulfonyloxy, or C_{6-41} aryloxy;



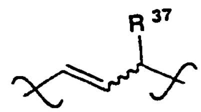
(vii)

wherein R^{35} is H, halide, hydroxy, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-12} alkoxy, C_{1-6} acyloxy, C_{1-6} acyl, C_{6-41} aryl, C_{3-40} heterocyclic radical, C_{3-40} heteroaryl, C_{1-12} alkylsulfonyloxy, C_{1-12} haloalkylsulfonyloxy, C_{6-40} arylsulfonyloxy, or C_{6-41} aryloxy;



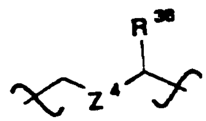
(viii)

wherein R^{36} is H, halide, hydroxy, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-12} alkoxy, C_{1-6} acyloxy, C_{1-6} acyl, C_{6-41} aryl, C_{3-40} heterocyclic radical, C_{3-40} heteroaryl, C_{1-12} alkylsulfonyloxy, C_{1-12} haloalkylsulfonyloxy, C_{6-40} arylsulfonyloxy, or C_{6-41} aryloxy;



(ix)

wherein R^{37} is H, C_{1-8} alkyl, (C_{6-40} aryl)(C_{0-6} alkyl), or (C_{3-10} heteroaryl)(C_{0-6} alkyl), (C_{3-10} heterocyclic radical)(C_{0-6} alkyl); and



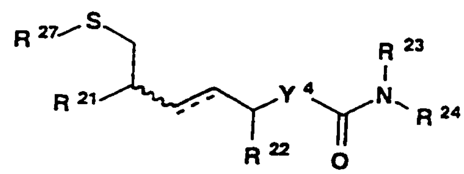
(x)

wherein R^{38} is H, C_{1-8} alkyl, (C_{6-40} aryl)(C_{0-6} alkyl), (C_{3-10} heterocyclic radical)(C_{0-6} alkyl), or (C_{3-10} heteroaryl)(C_{0-6} alkyl); and Z^4 is O, S, SO, SO_2, or NR^{39} wherein R^{39} is H, C_{1-6} alkyl, C_{1-6} acyl, (C_{6-40} aryl)-(C_{0-6} alkyl), (C_{3-12} heterocyclic radical)(C_{0-6} alkyl), (C_{3-10} heteroaryl)(C_{0-6} alkyl), or C_{2-14} alkyloxycarbonyl; or wherein R^{38} and NR^{39} taken together form a bifunctional C_{6-40} aryl, a bifunctional C_{3-12} heterocyclic radical, or a bifunctional C_{3-12} heteroaryl; and

R^{27} is H; a thiol protecting group; or a moiety set forth in the above generic formula (IV) wherein R^{27} is deleted, said compound being a symmetrical disulfide dimer or an asymmetrical disulfide;

or a pharmaceutically acceptable salt thereof.

5. A compound of claim 4, having the following formula:



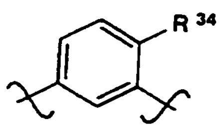
(V)

wherein R^{21} is H, NH_2, or NHR^{28}, R^{28} being C_{1-6} alkyl, C_{1-6} acyl, or C_{2-14} alkyloxycarbonyl;

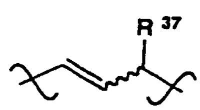
R^{23} is H or methyl;

R^{24} is $R^{25}(CH-)(C=O)R^{26}$, $R^{25}(CH-)(C=S)R^{26}$, or $R^{25}(CH_2-)$; and

Y^4 is selected from the following three formulae:

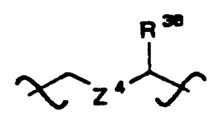


(xi)



(xii)

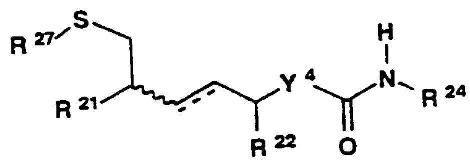
and



(xiii)

wherein Z^4 is O, S, or NR^{39}, wherein R^{39} is H, C_{1-6} alkyl, or C_{1-6} acyl; or wherein R^{38} and NR^{39} taken together form a bifunctional C_{6-40} aryl, a bifunctional C_{3-12} heterocyclic radical, or a bifunctional C_{3-12} heteroaryl.

6. A compound of claim 4, having the following formula:



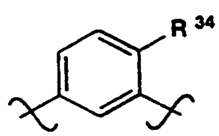
(VI)

wherein R^{21} is NH_2 or NHR^{28}, R^{28} being C_{1-6} alkyl, C_{1-6} acyl, or C_{2-14} alkyloxycarbonyl;

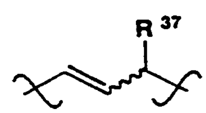
R^{22} is H or C_{1-8} alkyl;

R^{24} is C_{3-16} heterocyclic radical, C_{3-16} heteroaryl, $R^{25}(CH-)(C=O)R^{26}$, or $R^{25}(CH-)(C=S)R^{26}$, wherein R^{25} is C_{1-6} alkyl, hydroxymethyl, $-(CH_2)_n-A^4-(CH_2)_m-CH_3$, $-(CH_2)_n(C=O)NH_2$, or $-(CH_2)_n(C=O)NH(CH_2)_mCH_3$ (wherein A^4 is O, S, SO, or SO_2, n is 0, 1, or 2, and m is 0 or 1), or any other side chain of a naturally occurring amino acid, and R^{32} is H, C_{1-6} alkyl, or $(C_{1-12}$ acyl)oxy(C_{1-12} alkyl); and

Y^4 is selected from the following three formulae:

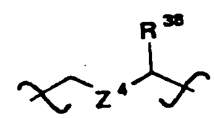


(xiv)



(xv)

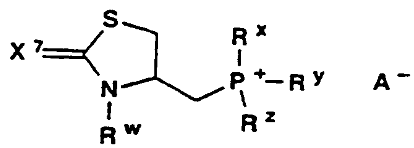
and



(xvi)

wherein Z^4 is O, S, or NR^{39}, wherein R^{39} is H, C_{1-6} alkyl, or C_{1-6} acyl; or wherein R^{38} and NR^{39} taken together form a bifunctional C_{6-40} aryl, a bifunctional C_{3-12} heterocyclic radical, or a bifunctional C_{3-12} heteroaryl.

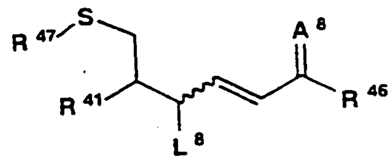
7. A compound having the following formula:



(VII)

wherein X^7 is O or S; R^W is H, C_{1-8} alkyl, C_{1-8} acyl, or C_{2-14} alkyloxycarbonyl; each of R^x, R^y, and R^z, independently, is C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{6-20} aryl, (C_{6-20} aryl)-(C_{1-12} alkyl), or (C_{1-12} alkyl)(C_{6-20} aryl); and A^- is a counterion.

8. A compound having the following formula:



(VIII)

wherein R^{41} is H, NH_2, NHR^{42}, or $NR^{42}R^{43}$, wherein R^{42} is C_{1-6} alkyl, C_{1-6} acyl, C_{2-14} alkyloxycarbonyl, or any other amino-protecting group, and R^{43} is C_{1-6} alkyl, C_{1-6} acyl, C_{2-14} alkyloxycarbonyl or, when taken together with R^{47}, is a bifunctional thiol-protecting group;

L^8 is halide, hydroxy, C_{1-12} alkoxy, C_{1-12} alkylsulfonyl-oxy, C_{6-20} arylsulfonyloxy, C_{1-12} acyloxy, C_{1-12} carbamoyl, or any other activated leaving group;

A^8 is =O, =S, or two singly-bonded H;

R^{46} is H, NH_2, NHOH, C_{3-10} heterocyclic radical, C_{3-10} heteroaryl, NHR^{44}, $NR^{44}R^{45}$, OR^{48}, $NR^{44}OR^{45}$, $NHOR^{49}$, or any other carboxyl-protecting group, wherein each of R^{44} and R^{45}, independently, is C_{1-6} alkyl, (C_{6-12} aryl)(C_{0-6} alkyl), (C_{3-16} heterocyclic radical)(C_{0-6} alkyl), (C_{3-16} heteroaryl)-(C_{0-6} alkyl), or C_{2-14} alkyloxycarbonyl, R^{48} is H, C_{1-6} alkyl, (C_{1-12} acyl)oxy(C_{1-12} alkyl), (C_{1-12} alkyl)oxy(C_{1-12} alkyl), or any other carboxyl- or hydroxyl-protecting group, and R^{49} is H, or C_{1-6} alkyl, provided that where A^8 is two singly-bonded H, R^{46} is such that the C atom bonded to both A^8 and R^{46} is bonded to either a N or O atom of R^{46}; and

R^{47} is H; a thiol-protecting group or, when taken together with R^{43}, a bifunctional thiol-protecting group; or a moiety set forth in the above generic formula (VIII) wherein R^{47} is deleted, said compound being a symmetrical disulfide dimer or an asymmetrical disulfide.

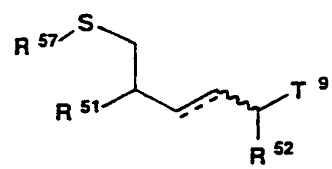
9. A compound of claim 8, wherein R^{41} is H, NH_2, NHR^{42}, or $NR^{42}R^{43}$, wherein R^{42} is C_{1-6} alkyl, C_{1-6} acyl, C_{2-14} alkyloxycarbonyl, or any other amino-protecting group, and R^{43} is C_{1-6} alkyl, C_{1-6} acyl, C_{2-14} alkyloxycarbonyl or, when taken together with R^{47}, is a bifunctional thiol-protecting group;

L^8 is halide, hydroxy, C_{1-7} alkoxy, C_{1-7} alkylsulfonyloxy, C_{6-12} arylsulfonyloxy, C_{1-12} acyloxy, or C_{1-12} carbamoyl, or any other activated leaving group;

R^{46} is H, NH_2, NHOH, C_{3-10} heterocyclic radical, C_{3-10} heteroaryl, NHR^{44}, $NR^{44}R^{45}$, OR^{48}, $NR^{44}OR^{45}$, $NHOR^{49}$, or any other carboxyl-protecting group, wherein each of R^{44} and R^{45}, independently, is C_{1-6} alkyl, (C_{6-10} aryl)(C_{0-3} alkyl), (C_{3-10} heterocyclic radical)(C_{0-3} alkyl), or (C_{3-10} heteroaryl)(C_{0-3} alkyl), R^{48} is H, C_{1-6} alkyl, (C_{1-7} acyl)oxy(C_{1-6} alkyl), (C_{1-6} alkyl)oxy(C_{1-6} alkyl), or any other carboxyl- or hydroxyl-protecting group, and R^{49} is H, or C_{1-6} alkyl, provided that where A^8 is two singly-bonded H, R^{46} is such that the C atom bonded to both A^8 and R^{46} is bonded to either a N or O atom of R^{46}; and

R^{47} is H; a thiol-protecting group or, when taken together with R^{43}, a bifunctional thiol-protecting group; or a moiety set forth in the above generic formula (VIII) wherein R^{47} is deleted, said compound being a symmetrical disulfide dimer or an asymmetrical disulfide.

10. A compound having the following formula:

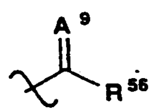


(IX)

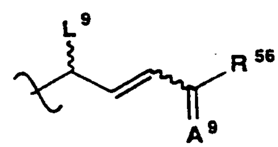
wherein R^{51} is H, NHR^{53}, or $NR^{53}R^{54}$, wherein R^{53} is H, C_{1-6} alkyl, C_{1-6} acyl, C_{2-14} alkyloxycarbonyl, or any other amino-protecting group, and R^{54} is C_{1-6} alkyl, C_{1-6} acyl, C_{2-14} alkyloxycarbonyl or, when taken together with R^{57}, a bifunctional thiol-protecting group;

R^{52} is H, C_{1-8} alkyl, (C_{6-40} aryl)(C_{0-6} alkyl), or (C_{3-10} heteroaryl)(C_{0-6} alkyl);

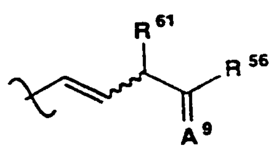
T^9 is selected from the following four formulae:



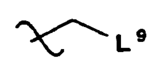
(xvii)



(xviii)



(xix) and



(xx)

wherein L^9 is halide, hydroxy, C_{1-12} alkoxy, C_{1-12} alkylsulfonyloxy, C_{6-20} arylsulfonyloxy, C_{1-12} acyloxy, C_{1-12} carbamoyl, or any other activated leaving group;

A^9 is =O, =S, or two singly-bonded H;

R^{56} is H, NH_2, NHOH, C_{3-10} heterocyclic radical,

C_{3-10} heteroaryl, NHR^{55}, $NR^{55}R^{58}$, OR^{59}, $NR^{55}OR^{58}$, $NHOR^{60}$, or any other carboxyl-protecting group, wherein each R^{55} and R^{58}, independently, is C_{1-6} alkyl, (C_{6-12} aryl)(C_{0-6} alkyl), (C_{3-16} heterocyclic radical)(C_{0-6} alkyl), (C_{3-16} heteroaryl)-(C_{0-6} alkyl), or C_{2-14} alkyloxycarbonyl, R^{59} is H, C_{1-6} alkyl, (C_{1-12} acyl)oxy(C_{1-12} alkyl), or (C_{1-12} alkyl)oxy-(C_{1-12} alkyl), and R^{60} is H or C_{1-6} alkyl; provided that where A^9 is two singly-bonded H, R^{56} is selected such that the carbon atom bonded to both A^9 and R^{56} is bonded to either a nitrogen or oxygen atom of R^{56};

R^{61} is H, C_{1-8} alkyl, (C_{6-40} aryl)(C_{0-6} alkyl), or (C_{3-10} heteroaryl)(C_{0-6} alkyl); and

R^{57} is H; a thiol-protecting group or, taken together with R^{54}, a bifunctional thiol-protecting group; or a moiety set forth in the above generic formula (IX) wherein R^{57} is deleted, said compound being a symmetrical disulfide dimer or an asymmetrical disulfide.

11. A compound of claim 10, wherein R^{51} is H, NHR^{53}, or $NR^{53}R^{54}$, wherein R^{53} is H, C_{1-6} alkyl, C_{1-6} acyl, C_{2-14} alkyloxycarbonyl, or any other amino-protecting group, and R^{54} is C_{1-6} alkyl, C_{1-6} acyl, C_{2-14} alkyloxycarbonyl or, when taken together with R^{57}, a bifunctional thiol-protecting group;

R^{52} is H, C_{1-8} alkyl, (C_{6-10} aryl)(C_{0-3} alkyl), or (C_{3-10} heteroaryl)(C_{0-3} alkyl);

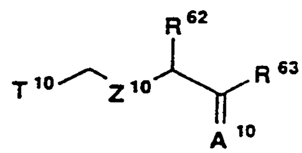
wherein L^9 is halide, hydroxy, C_{1-7} alkoxy, C_{1-6} alkylsulfonyloxy, C_{6-10} arylsulfonyloxy, C_{1-7} acyloxy, C_{1-7} carbamoyl, or any other activated leaving group;

R^{56} is H, NH_2, NHOH, C_{3-8} heterocyclic radical, C_{3-8} heteroaryl, NHR^{55}, $NR^{55}R^{58}$, OR^{59}, $NR^{55}OR^{58}$, $NHOR^{60}$, or any other carboxyl-protecting group, wherein each R^{55} and R^{58}, independently, is C_{1-6} alkyl, (C_{6-10} aryl)(C_{0-3} alkyl), (C_{3-10} heterocyclic radical)(C_{0-3} alkyl), or (C_{3-10} heteroaryl)(C_{0-3} alkyl), R^{59} is H, C_{1-6} alkyl, (C_{1-7} acyl)oxy(C_{1-7} alkyl), (C_{1-7} alkyl)oxy(C_{1-7} alkyl), or C_{2-14} alkyoxycarbonyl, and R^{60} is H or C_{1-6} alkyl; provided that where A^9 is two singly-bonded H, R^{56} is selected such that the carbon atom bonded to both A^9 and R^{56} is bonded to either a nitrogen or oxygen atom of R^{56};

R^{61} is H, C_{1-8} alkyl, (C_{6-20} aryl)(C_{0-3} alkyl), or (C_{3-10} heteroaryl)(C_{0-3} alkyl); and

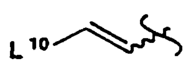
R^{57} is H; a thiol-protecting group or, when taken together with R^{54}, a bifunctional thiol-protecting group; or a moiety set forth in the above generic formula (IX) wherein R^{57} is deleted, said compound being a symmetrical disulfide dimer.

12. A compound having the following formula:

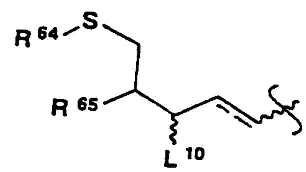


(X)

wherein T^{10} is selected from the following three formulae:

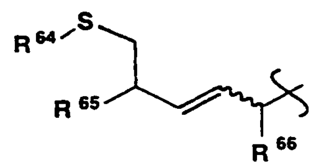


(xxi)



(xxii)

and



(xxiii)

wherein L^{10} is halide, C_{1-12} alkoxy, C_{1-12} alkylsulfonyloxy, C_{6-20} arylsulfonyloxy, C_{1-12} acyloxy, C_{1-12} carbamoyl, or any other activated leaving group; R^{65} is H, NH_2, NHR^{67}, or $NR^{67}R^{68}$, wherein R^{67} is C_{1-6} alkyl, C_{1-6} acyl, C_{2-14} alkyloxycarbonyl or any other amino-protecting group, and R^{68} is C_{1-6} alkyl, C_{1-6} acyl, C_{2-14} alkyloxycarbonyl or, when taken together with R^{64}, a bifunctional thiol-protecting group; R^{64} is H; a thiol-protecting group or, when taken together with R^{68}, a bifunctional thiol-protecting group; or a moiety set forth in the above generic formula (X) wherein R^{64} is deleted, said compound being a symmetrical disulfide dimer or an asymmetrical disulfide;

R^{66} is H, C_{1-8} alkyl, $(C_{6-40}$ aryl$)(C_{0-6}$ alkyl$)$, or

(C_{3-10} heteroaryl)(C_{0-6} alkyl);

R^{63} is H, NH_2, NHOH, C_{3-10} heterocyclic radical, C_{3-10} heteroaryl, NHR^{69}, $NR^{69}R^{70}$, OR^{71}, $NR^{69}OR^{70}$, $NHOR^{72}$, or any other carboxyl-protecting group, wherein each of R^{69} and R^{70}, independently, is C_{1-6} alkyl, (C_{3-16} heterocyclic radical)-(C_{0-6} alkyl), or (C_{3-16} heteroaryl)(C_{0-6} alkyl), R^{71} is H, C_{1-6} alkyl, (C_{1-12} acyl)oxy(C_{1-12} alkyl), or (C_{1-12} alkyl)oxy(C_{1-12} alkyl), and R^{72} is H or C_{1-6} alkyl; provided that where A^{10} is two singly-bonded H, R^{63} is selected such that the carbon atom bonded to both A^{10} and R^{63} is bonded to either a nitrogen or oxygen atom of R^{63};

A^{10} is O, S, or two singly-bonded H; and

R^{62} is H, C_{1-8} alkyl, (C_{6-40} aryl)(C_{0-6} alkyl), (C_{3-10} heterocyclic radical)(C_{0-6} alkyl), or (C_{3-10} heteroaryl)(C_{0-6} alkyl); and Z^{10} is O, S, SO, SO_2, or NR^{73} wherein R^{73} is H, C_{1-6} alkyl, C_{1-6} acyl, (C_{6-40} aryl)-(C_{0-6} alkyl), (C_{3-10} heteroaryl)(C_{0-6} alkyl), or C_{2-14} alkyloxycarbonyl.

13. A compound of claim 12, wherein L^{10} is halide, C_{1-7} alkoxy, C_{1-7} alkylsulfonyloxy, C_{6-10} arylsulfonyloxy, C_{1-7} acyloxy, C_{1-7} carbamoyl, or any other activated leaving group;

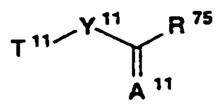
R^{65} is H, NH_2, NHR^{67}, or $NR^{67}R^{68}$, wherein R^{67} is C_{1-6} alkyl, C_{1-6} acyl, C_{2-14} alkyloxycarbonyl or any other amino-protecting group, and R^{68} is C_{1-6} alkyl, C_{1-6} acyl, C_{2-14} alkyloxycarbonyl or, when taken together with R^{64}, a bifunctional thiol-protecting group; R^{64} is H; a thiol-protecting group or, when taken together with R^{68}, a bifunctional thiol-protecting group; or a moiety set forth in the above generic formula (X) wherein R^{64} is deleted, said compound being a symmetrical disulfide dimer or an asymmetrical disulfide;

R^{66} is H, C_{1-8} alkyl, $(C_{6-20}$ aryl$)(C_{0-3}$ alkyl$)$, or $(C_{3-10}$ heteroaryl$)(C_{0-3}$ alkyl$)$;

R^{63} is H, NH_2, NHOH, C_{3-10} heterocyclic radical, C_{3-10} heteroaryl, NHR^{69}, $NR^{69}R^{70}$, OR^{71}, $NR^{69}OR^{70}$, $NHOR^{72}$, or any other carboxyl-protecting group, wherein each of R^{69} and R^{70}, independently, is C_{1-6} alkyl, $(C_{3-10}$ heterocyclic radical$)$-$(C_{0-3}$ alkyl$)$, or $(C_{3-10}$ heteroaryl$)(C_{0-3}$ alkyl$)$, R^{71} is H, C_{1-6} alkyl, $(C_{1-7}$ acyl$)$oxy$(C_{1-6}$ alkyl$)$, or $(C_{1-6}$ alkyl$)$oxy$(C_{1-6}$ alkyl$)$, and R^{72} is H or C_{1-6} alkyl; provided that where A^{10} is two singly-bonded H, R^{63} is selected such that the carbon atom bonded to both A^{10} and R^{63} is bonded to either a nitrogen or oxygen atom of R^{63}; and

R^{62} is H, C_{1-8} alkyl, $(C_{6-20}$ aryl$)(C_{0-3}$ alkyl$)$, $(C_{3-10}$ heterocyclic radical$)(C_{0-3}$ alkyl$)$, or $(C_{3-10}$ heteroaryl$)(C_{0-3}$ alkyl$)$; and Z^{10} is O, S, SO, SO_2, or NR^{73} wherein R^{73} is H, C_{1-6} alkyl, C_{1-6} acyl, $(C_{6-20}$ aryl$)$-$(C_{0-3}$ alkyl$)$, $(C_{3-10}$ heteroaryl$)(C_{0-3}$ alkyl$)$, or C_{2-14} alkyloxycarbonyl.

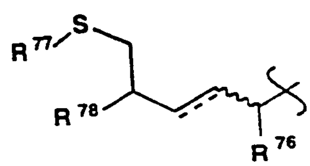
14. A compound having the following formula:



(XI)

wherein:

T^{11} is selected from H-(C=O)-, H-(C=O)-CH(R^{76})-,



(xxiv)

and

(xxv)

wherein

R^{75} is H, NH_2, NHOH, C_{3-16} heterocyclic radical, C_{3-16} heteroaryl, NHR^{81}, $NR^{81}R^{82}$, OR^{83}, $NR^{81}OR^{82}$, $NHOR^{84}$ or any other carboxyl-protecting group, wherein each R^{81} and R^{82}, independently, is C_{1-6} alkyl, (C_{6-12} aryl)(C_{0-6} alkyl), (C_{3-16} heterocyclic radical)(C_{0-6} alkyl), or (C_{3-16} heteroaryl)(C_{0-6} alkyl), R^{83} is H, C_{1-6} alkyl, (C_{1-12} acyl)oxy(C_{1-12} alkyl), or (C_{1-12} alkyl)oxy-(C_{1-12} alkyl), and R^{84} is H, or C_{1-6} alkyl;

R^{76} is H, C_{1-8} alkyl, (C_{6-40} aryl)(C_{0-6} alkyl), or (C_{3-10} heteroaryl)(C_{0-6} alkyl);

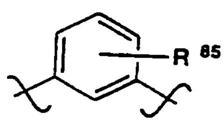
R^{77} is H; a thiol-protecting group or, when taken together with R^{80}, a bifunctional thiol-protecting group; or a moiety set forth in the above generic formula (XI) wherein R^{77} is deleted, said compound being a symmetrical disulfide dimer or an asymmetrical disulfide;

R^{78} is H, NH_2, NHR^{79}, or $NR^{79}R^{80}$, wherein R^{79} is

C_{1-6} alkyl, C_{1-6} acyl, C_{2-14} alkyloxycarbonyl or any other amino-protecting group, and R^{80} is C_{1-6} alkyl, C_{1-6} acyl, C_{2-14} alkyloxycarbonyl or, when taken together with R^{77}, a bifunctional thiol-protecting group;

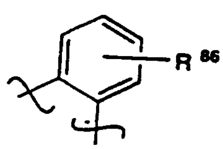
L^{11} is halide, C_{1-12} alkylsulfonyloxy, C_{6-20} arylsulfonyloxy, C_{2-12} alkylcarbonyloxy, or any other activated leaving group;

Y^{11} is selected from the following three formulae:



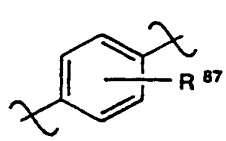
(xxvi)

wherein R^{85} is H, halide, hydroxy, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-12} alkoxy, C_{1-6} acyloxy, C_{1-6} acyl, C_{6-41} aryl, C_{3-40} heterocyclic radical, C_{3-40} heteroaryl, C_{1-12} alkylsulfonyloxy, C_{1-12} haloalkylsulfonyloxy, C_{6-40} arylsulfonyloxy, or C_{6-41} aryloxy;



(xxvii)

wherein R^{86} is H, halide, hydroxy, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-12} alkoxy, C_{1-6} acyloxy, C_{1-6} acyl, C_{6-41} aryl, C_{3-40} heterocyclic radical, C_{3-40} heteroaryl, C_{1-12} alkylsulfonyloxy, C_{1-12} haloalkylsulfonyloxy, C_{6-40} arylsulfonyloxy, or C_{6-41} aryloxy; and



(xxviii)

wherein R^{87} is H, halide, hydroxy, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-12} alkoxy, C_{1-6} acyloxy, C_{1-6} acyl, C_{6-41} aryl, C_{3-40} heterocyclic radical, C_{3-40} heteroaryl, C_{1-12} alkylsulfonyloxy, C_{1-12} haloalkylsulfonyloxy, C_{6-40} arylsulfonyloxy, or C_{6-41} aryloxy; and

A^{11} is O, S, or two singly-bonded H.

15. A compound of claim 14, wherein R^{75} is H, NH_2, NHOH, (C_{3-10} heterocyclic radical)(C_{0-3} alkyl), (C_{3-10} heteroaryl)-(C_{0-3} alkyl), NHR^{81}, $NR^{81}R^{82}$, OR^{83}, $NR^{81}OR^{82}$, $NHOR^{84}$ or any other carboxyl-protecting group, wherein each R^{81} and R^{82}, independently, is C_{1-6} alkyl, (C_{6-10} aryl)(C_{0-3} alkyl), (C_{3-10} heterocyclic radical)(C_{0-3} alkyl), or (C_{3-10} heteroaryl)(C_{0-3} alkyl), R^{83} is H, C_{1-6} alkyl, (C_{1-7} acyl)oxy(C_{1-6} alkyl), or (C_{1-6} alkyl)oxy-(C_{1-6} alkyl), and R^{84} is H, or C_{1-6} alkyl;

R^{76} is H, C_{1-8} alkyl, (C_{6-20} aryl)(C_{0-3} alkyl), or (C_{3-10} heteroaryl)(C_{0-3} alkyl);

R^{77} is H; a thiol-protecting group or, when taken together with R^{80}, a bifunctional thiol-protecting group; or a moiety set forth in the above generic formula (XI) wherein R^{77} is deleted, said compound being a symmetrical disulfide dimer;

R^{78} is H, NH_2, NHR^{79}, or $NR^{79}R^{80}$, wherein R^{79} is C_{1-6} alkyl, C_{1-6} acyl, C_{2-14} alkyloxycarbonyl or any other amino-protecting group, and R^{80} is C_{1-6} alkyl, C_{1-6} acyl, C_{2-14} alkyloxycarbonyl or, when taken together with R^{77}, a bifunctional thiol-protecting group;

L^{11} is halide, C_{1-6} alkoxy, C_{1-6} alkylsulfonyloxy, C_{6-10} arylsulfonyloxy, C_{1-7} acyloxy, C_{1-7} carbamoyl, or any other activated leaving group; and

R^{85} is H, halide, hydroxy, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-7} alkoxy, C_{1-6} acyloxy, C_{1-6} acyl, C_{6-20} aryl, C_{3-16} heterocyclic radical, C_{3-16} heteroaryl, C_{1-6} alkylsulfonyloxy, C_{1-6} haloalkylsulfonyloxy, C_{6-20} arylsulfonyloxy, or C_{6-20} aryloxy.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/03387

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :Please See Extra Sheet.
US CL :548/182, 201; 549/77; 560/16, 51, 153; 562/426,556; 564/154
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
U.S. : 548/182, 201; 549/77; 560/16, 51, 153; 562/426,556; 564/154

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 5,238,922 (GRAHAM ET AL) 24 August 1993, columns 3 and 4.	1-6, 8-15
Y, P	WO, A, 94/09766 (DESOLMS ET AL) 11 May 1994, page 7.	1-6, 8-15
Y	The Journal of Biological Chemistry, Volume 268, No. 28, issued 05 October 1993, M. Nigram et al., "Potent Inhibition of Human Tumor p21(ras) Farnesyltransferase by A1A2-lacking p21(ras) CA1A2X Peptidomimetics", pages 20695-20698, especially page 20696.	1-6,8-15
A, P	US, A, 5,340,828 (GRAHAM ET AL) 23 August 1994.	1-15

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search 09 JUNE 1995	Date of mailing of the international search report 14 JUL 1995
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer Della Collins for BARBARA FRAZIER Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/03387

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☒ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/03387

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):

C07C237/20, 317/10, 317/24, 317/28, 317/50, 321/10, 323/22, 323/29, 323/56; C07D 277/04, 277/12, 333/22

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

I. Claims 1-7, drawn to an S,N-containing compound (claims 1-6) and a phosphonium intermediate (claim 7).
II. Claims 8 and 9, drawn to intermediate compounds containing an activated leaving group three carbons removed from the sulfur and a double bond four to five carbons removed from the sulfur.
III. Claims 10 and 11, drawn to intermediate compounds containing an optional double bond three to four carbons removed from the sulfur.
IV. Claims 12 and 13, drawn to intermediate compounds containing a carboxyl protecting group (R63).
V. Claims 14 and 15, drawn to intermediate compounds containing an interphenylene group.

The inventions listed as Groups I-V do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the different intermediate products do not have the same essential structural element, and the application claims different intermediates for different structural parts of the final product.